Bayesian spatio-temporal modelling of malaria surveillance in Uganda

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Basel, den 26 Juni 2018

Prof. Dr. Martin Spiess
Dekan

…to my beloved late mother, **Sperancia Mukagatare**

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List of Abbreviations

ACTs	Artemisinin-based Combination Therapies
BCI	Bayesian Credible Interval
CDC	Centre for Diseases Control
CAR	Conditional Autoregressive
LSTD	Day Land Surface Temperature
DHS	Demographic Health Survey
DIC	Deviance Information Criterion
DDT	Dichlorodiphenyltrichloroethane
DALYs	Disability Adjusted Lost Years
DHIS2	District Health Information Software System version 2
EIR	Entomological Inoculation Rate
EWES	Environmental Monitoring System
Global Fund	Global Fund to Fight AIDS, tuberculosis, and malaria
GMEC	Global Malaria Eradication Campaign
GRUMP	Global Rural-Urban Mapping Project
HC	Health Centre
HMIS	Health Management Information System
HSSP	Health Sector Strategic and Investment Plan development plan
HCT	HIV Counseling and Testing
IRS	Indoor Residual Spraying
IEC	Information, Education and Communication
ITNs	Insecticide Treated Nets
IDSR	Integrated Disease Surveillance and Response
INLA	Integrated Nested Laplace Approximation
IPTp	Intermittent Preventive Treatment of pregnant women
ICF	International Consulting Firm
MEWS	Malaria Early Warning System
MIS	Malaria Indicator Surveys
MCMC	Markov chain Monte Carlo
MoH	Ministry of Health
MODIS	Moderate Resolution Imaging Spectroradiometer
MCA	Multiple Correspondence Analysis
NMCP	National Malaria Control Program
NMA	National Meteorological Authority
LSTN	Night Land Surface Temperature
NCDs	Non-Communicable Diseases
NDVI	Normalized Difference Vegetation Index
OR	Odds Ratio
OpenMRS	Open Medical Records Systems
PCR	Polymerase Chain Reaction
PMI	Presidential Malaria Initiative
RDTs	Rapid Diagnostic Tests

RBM	Roll Back Malaria
SSA	Saharan Africa
SRTM	Shuttle Radar Topographic Mission
USGSS	U.S. Geological Survey-Earth Resources Observation Systems
UBOS	Uganda Bureau of Statistics
UMRSP	Uganda Malaria Reduction Strategic Plan
UNCST	Uganda National Council for Science and Technology
USDI	Uganda Service Delivery Indicator
USAID	United States Aid for International Development
VHT	Village Health Teams
WHO	World Health Organization

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Summary

Malaria is one of the oldest infectious diseases that has had global health significance on humans for several centuries. In recent times, its burden has been concentrated in the Sub-Sahara Africa (SSA) region where almost 90% of the global malaria morbidity and mortality burden is shouldered. In these countries, transmission is high mainly due to suitable weather conditions, yet control and prevention activities are hampered by weak national health systems and low socioeconomic development. This situation leads to a significant loss of lives in endemic countries particularly in the vulnerable groups of children less than 5 years and pregnant women, as well as pain, suffering, and economic losses due to lost workdays. This further undermines socioeconomic development and perpetuates the vicious cycle of poverty in the affected countries. Uganda ranks number four among the 15 high-burdened countries, with the disease being the leading cause of hospitalization and death.

The launch of Roll Back Malaria (RBM) initiative in the mid-2000s heralded renewed global interest and financial investment towards malaria control and elimination leading to accelerated scale-up of proven malaria control, prevention, and treatment interventions. These interventions are; Insecticide Treated Nets (ITNs), Indoor Residual Spraying (IRS), and case management with Artemisinin-based Combination Therapies (ACTs). The scale-up has been followed by a decline in malaria burden in Uganda and other endemic countries. This increased financial support has also been extended to malaria surveillance, specifically in the strengthening of the national Health Management Information System (HMIS) used for routine reporting of health facility data, and the implementation of nationally representative household surveys and facility assessment surveys. The routine data facilitates the assessment of inter and intra annual variation of malaria burden in the country, whereas data from the national household surveys are spatially structured and therefore can be used to identify the population groups and areas most

affected as well as track the progress of malaria interventions coverage at national and subnational scale.

Despite the availability of these rich data, their utilization remains low in the country. The information extracted from surveillance data by the Ministry of Health (MoH) and National Malaria Control Program (NMCP) is limited to national averages that neither take into account subnational heterogeneities and disparities nor evaluate the effects of interventions on malaria burden changes in space and time. This is because the standard statistical methods are ill-suited for analysis of malaria surveillance data, yet NMCP lack the capacity to develop and apply the advanced state-of-the-art methods appropriate for such data. For instance, the usual statistical assumption of independence of data observations in standard statistical software does not hold for malaria surveillance data due to the presence of spatial correlation arising out of similarity of common exposures such as the environment and the mosquito flying distance in neighboring areas. Also, the longitudinal nature of routine data introduces temporal correlation due to proximal time points. Failure to take into account spatial and temporal correlation in inference results in incorrect estimates of the risk, imprecise predictor effects, and erroneous predictions and forecasts that are necessary for surveillance.

Bayesian hierarchical geostatistical and spatio-temporal models fitted via Markov Chain Monte Carlo (MCMC) simulations are flexible to incorporate correlations in time and space and can be easily extended to capture complex relationships. They can accurately estimate malaria burden at high spatial resolution, assess interventions and health system-related effects, and can support Early Warning Systems (EWS) for effective surveillance.

The objectives of this thesis is to develop Bayesian spatio-temporal models for malaria surveillance in Uganda, to i) assess the effect of interventions on the geographical distribution of malaria prevalence in the country; ii) determine the contribution of interventions on spatio-temporal changes of parasitaemia risk; iii) estimate the effects of interventions on space-time

patterns of malaria incidence; iv) investigate interactions between climatic changes and intervention effects on malaria incidence spatio-temporal dynamics; v) assess the role of health facility readiness on severe malaria outcomes; and vi) develop forecasting models to support malaria early warning system in the country.

In Chapter 2, Bayesian geostatistical models with spatially varying coefficients were developed to determine the interventions' effects on malaria prevalence in 2014 at national and subnational levels and to predict malaria risk at unsampled locations. Interventions had a significant but varying protective effect on malaria prevalence. The highest prevalence was predicted for regions of East Central, North East, and West Nile, whereas the lowest prevalence was predicted in Kampala and South Western regions.

In Chapter 3, Bayesian geostatistical and temporal models were applied on Malaria Indicator Survey (MIS) data of 2009 and 2014 to quantify the effects of interventions on spatio-temporal changes of parasitaemia risk during 2009-2014. The models took into account geographical misalignment in the locations of the surveys. During this period, the coverage of interventions more than doubled, and interventions had a strong effect on the decline of parasitaemia risk, albeit with varying magnitude in the regions. The estimated number of children <5 years infected with malaria declined from 2,480,373 to 825,636.

We developed Bayesian spatio-temporal negative binomial models in Chapter 4 to assess the effects of case management with artemisinin combination therapies and vector-control interventions on space-time patterns of malaria incidence using HMIS data reported during 2013-2016. Heterogeneity in incidence was taken into account via year-specific, spatially structured and unstructured random effects modeled at district level via Conditional Autoregressive (CAR) and Gaussian exchangeable prior distributions, respectively. The nested space–time structure allowed the geographical variation of malaria to vary from year to year. Temporal correlation across months was captured by monthly random effects modeled by an

autoregressive process of order 1 (AR1). Models were adjusted for seasonality by including Fourier terms as a mixture of two cycles with periods of 6 and 12 months, respectively. A yearly trend was fitted to estimate changes of the incidence rates over time. The temporal variation in incidence was similar in both age groups and depicted a steady decline from 2013 to 2014, followed by an increase in 2015. The trends were characterized by a strong bi-annual seasonal pattern with two peaks during May-July and September-December. Increases in interventions were associated with a reduction in malaria incidence in all age groups. The space-time patterns of malaria incidence in children < 5 years were similar to those of parasitaemia risk predicted from the MIS of 2014-15 in Chapter 3.

In Chapter 5 we assessed the relationship between climatic changes and their interactions with malaria interventions on changes in malaria incidence between 2013 and 2017. Bayesian spatio-temporal negative binomial CAR models were applied on district-aggregated monthly malaria cases reported in the District Health Information System version 2 (DHIS2) during 2013-2017. The models were adjusted for socioeconomic factors and treatment-seeking behaviour patterns. The annual average of rainfall, Day Land Surface Temperature (LSTD) and Night Land Surface Temperature (LSTN) increased whereas Normalized Difference Vegetation Index (NDVI) decreased. The increase in LSTD and decrease in NDVI were associated with a reduction in the incidence decline. Important interactions between interventions with NDVI and LSTD suggest a varying impact of interventions on malaria burden in different climatic conditions.

In Chapter 6, we linked USDI survey data of 2013 with severe malaria outcomes data reported in the Health Management Information System (HMIS) to construct a multidimensional readiness index for health facilities in Uganda. Bayesian geostatistical negative Binomial models were used to assess the effects of facility readiness on severe malaria incidence and mortality. The index was created using Multiple Correspondence Analysis (MCA) based on more than one

dimension of the most relevant general service and malaria service readiness indicators for severe malaria outcomes identified through stochastic variable selection. Exploiting more than one dimension in the multiple correspondence analysis produces a more robust index of facility readiness Malaria-specific readiness was achieved in only one quarter of the facilities. Malaria specific readiness was higher in HCIIIs and in private managed compared to HCIIs and government managed facilities. In both HCIIIs and HCIIs, mortality and incidence rates of severe malaria cases decreased with increasing facility readiness.

In chapter 7 we developed polynomial distributed lag models to forecast malaria cases in different malaria endemic settings in Uganda using weekly surveillance data of parasitologically confirmed malaria cases extracted from the Integrated Disease Surveillance and Response (IDSR) during 2013-2016 and remote sensing climatic data. We employed stochastic variable selection to identify the optimal order that provided the best description to the malaria-climate relationship in each endemic setting in Uganda. The developed models were used to estimate the distributed lag effect of climatic factors on malaria cases. The third and first order polynomial distributed lag models explained maximal variation in the low endemic and very high endemic settings, respectively, whereas the second order polynomial distributed lag model provided superior fit in the moderate and high endemic settings. Predictive performance at different lead times varied by endemic setting, but overall, the best predictive performance was produced in the moderate and high endemic settings. Rainfall was associated with a delayed increase and immediate decrease in malaria in low and moderate endemic settings, but an immediate increase in malaria in the high and very high endemic settings. Day LST was associated with an immediate decline in malaria followed by a delayed increase in low, moderate and high endemic settings, but an immediate increase in malaria in very high endemic settings.

The results of this work will inform decision making in priority setting, timing of targeted deployment of interventions to maximize benefits and optimize resources in order to achieve the milestones of the Uganda Malaria Reduction Strategic Plan (UMRSP) 2014-2020.

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I dedicate this thesis to my beloved late mother **Sperancia Mukagatare** (May the Lord grant her soul eternal rest) who first sowed in me the seeds of education and piety at an early age that laid the foundation for this achievement. In the same vein, I thank my brothers Donnie Rutaisire and the late Frank Rutabingwa, Maama Nyirabalela, and Kojja Ssebikamba for also contributing generously to my formative education. My heartfelt thanks also go to my fiancé Fatuma Namugga for her patience during all this time I was overseas. Equally I am indebted to my family for their prayers, support, love, and encouragement. In no particular order, I thank Maria S. Mukagatale, Joseph M. Balikuddembe, Simon P. Sseguya, John Baptist Ssempiira, Theresa Naiga, Josephine Naiga, Monday Vabostine, Carol Namatovu, Francis Nsengiyumva, Baaba Sarah, Muteteri, Godfrey Katende, Don Nkusi, Maama Mukanziga, Maama Munkakusi, David Mugambe Kibirango, John Kazungu, Paul Kamoga, Fauza Namutebi and Kojja Kanyenzi,.

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Chapter 1: Introduction

1.1 Background

Malaria is the most important infectious disease in the history of mankind dating back to ancient times when humans started living together in food-producing communities (Webb, 2009). Throughout the centuries malaria caused loss of life, pain and suffering to mankind yet it was only until after the second world war that global-level efforts - the Global Malaria Eradication Campaign (GMEC) - were undertaken by the World Health Organisation (WHO) to eliminate the disease (Snow and Marsh, 2010). This campaign which relied heavily on residual spraying of house walls with Dichlorodiphenyltrichloroethane (DDT) and treatment of cases with chloroquine antimalarial drugs was formally abandoned in 1969 after failing to achieve elimination in the least developed parts of the world especially in SSA owing to weak public health infrastructure and the emergence of insecticide and parasite resistance (Müller, 2011). This failure to control malaria in SSA continued unabated through decades and was later to turn into a public health disaster in the early 1990s with the emergence of HIV/AIDS pandemic, a combination which culminated into high morbidity and mortality rates unprecedented in the 20th century (White et al., 1999).

To halt the disastrous situation from further aggravation, the African Heads of states in conjunction with the leading international health initiatives launched the Roll Back Malaria (RBM) initiative at the Abuja Declaration summit of 1998 (Snow and Marsh, 2010). This marked the first serious international efforts to control, prevent and treat malaria in endemic countries of SSA unrivalled since the demise of GMEP. The major players in the RBM partnership include the US Presidential Malaria Initiative (PMI) and the Global Fund to Fight AIDS, tuberculosis, and malaria (Global Fund). These have made significant investments in malaria control and prevention resulting in accelerated scale-up of highly proven malaria interventions, namely, ITNs, IRS, and ACTs (Snow et al., 2015). These efforts have led to a global decline of malaria morbidity and mortality including in countries of high endemicity in

SSA (Bhatt et al., 2015a; Lengeler, 2004). For instance, during 2000-2015, the global malaria prevalence, incidence, and mortality declined by up to 24%, 41%, and 62%, respectively, and the number of people infected with malaria parasites in SSA declined from 131 million to 114 million (World Health Organisation, 2017). As a result, the number of countries with on-going malaria transmission reduced from 106 in 2000 to 91 in 2015, and malaria went down from the first to the fourth highest cause of mortality in children less than 5 years during 2000-2015 (World Health Organization, 2015a).

1.2 Species, vectors and transmission cycle

Malaria is transmitted to humans by female Anopheles mosquitoes. Although over 100 vectors are known to have the capacity to transmit malaria, the most dominant vectors are Anopheles gambiae complex (*An. gambiae sensu stricto, An. arabiensis, An. bwambae)* and *Anopheles funestus* (Wiebe et al., 2017). *A. gambiae* species complex is the most dominant species in SSA and most effective among all vectors and breeds in small temporary pools and puddles, while *A. funestus* is commonly found at higher altitudes and breeds mainly in permanent water bodies (Bass et al., 2007). Within the *A. gambiae* complex, *Anopheles gambiae s.s.* is the most common and is predominantly anthropophilic (feeds on humans) and endophilic (feeds indoors), hence making vector control strategies feasible for its control (The Anopheles gambiae 1000 Genomes Consortium, 2017).

Four protozoan parasites cause malaria in humans, namely, *Plasmodium falciparum, P. vivax, P.ovale*, and *P. malariae*, and most recently a fifth parasite, *P.knowles*, has been discovered which infects both humans and animals (Cox, 2010). *P. falciparum* is the most prevalent species in SSA and the most fatal in killing young children (Loy et al., 2017).

The parasite transmission cycle takes place in two stages; the asexual stage in the human host and the sexual stage in the vector. The asexual stage begins when an infected mosquito injects sporozoites into the body of a human host where they move to the liver cells where they undergo asexual multiplication leading to the production of merozoites. These move into the

bloodstream and invade the red blood cells when they undergo another cycle of asexual multiplication resulting in the production of 6-24 merozoites that again invade red blood cells. This process is repeated several times each time marked by a bout of fever caused by rupture of the red blood cells. During this course, some merozoites transform into male and female gametocytes that circulate in the bloodstream which are sucked by a mosquito during feeding. In the sexual stage, the gametocytes grow into male and female gametes. Fertilization follows leading to the formation of ookinete in the mosquito gut and this marks the beginning of sporogony. The ookinete goes into the gut wall of the mosquito and transforms into an oocyst and sets off another multiplication phase that results into formation of sporozoites that move to the salivary glands of the mosquito where they are inoculated into another human host at the next feeding (Cox, 2010).

1.3 Clinical features and malaria diagnosis

The most common symptoms of uncomplicated malaria are; fever, chills, headaches, perspiration, body weakness, general malaise, body aches, vomiting and nausea (Bartoloni and Zammarchi, 2012).

An enlarged spleen is also common in endemic countries. In addition, severe malaria may cause cardiovascular collapse and shock, anemia due to the destruction of red blood cells, and cerebral malaria which impairs consciousness leading to seizures and coma (Pasvol, 2005).

In the absence of other sensitive parasitological-based diagnostic techniques such as Rapid Diagnostic Tests (RDTs) and microscopy, diagnosis by clinical symptoms is less sensitive as most symptoms resemble those manifested by acute respiratory infections in young children (Luxemburger et al., 1998).

1.4 Malaria epidemiology

Despite the decline in malaria achieved following RBM-supported interventions scale-up since the mid-2000s, malaria remains a global public health challenge with over three billion people at

risk. In 2016 alone, malaria was responsible for over 216 million cases most of them in SSA (Figure 1.1) and over 438,000 deaths of which 90% occurred in children less than 5 years (World Health Organisation, 2017).

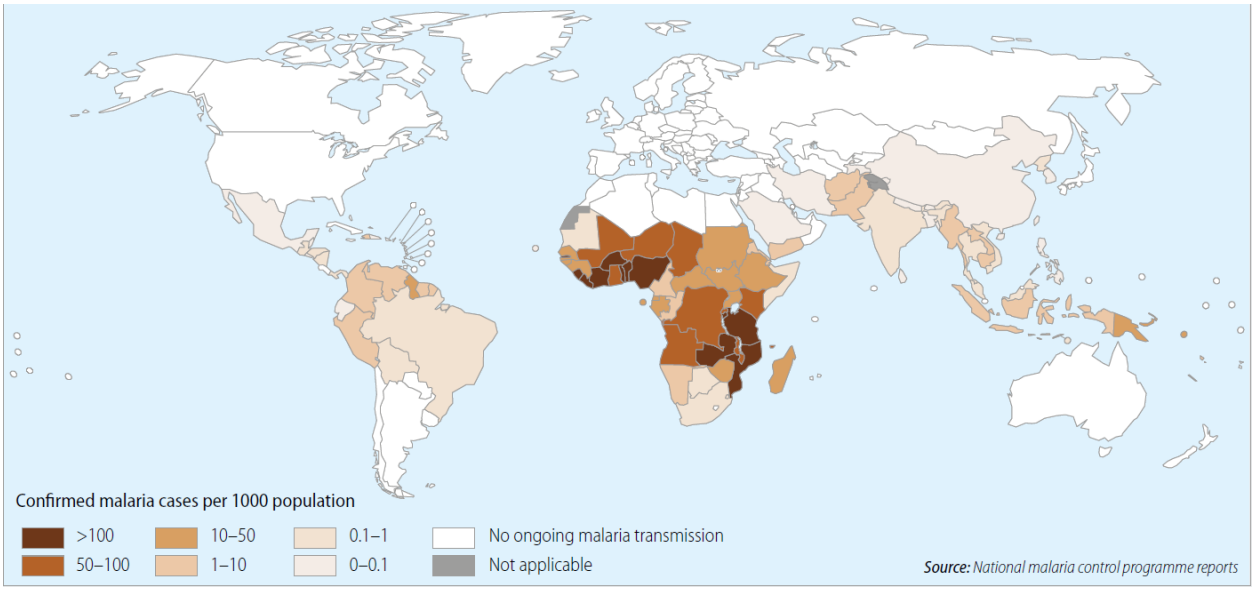

Figure 1.1: Global malaria burden distribution (source: World malaria report 2015)

In Uganda, malaria is ranked fourth among the 15 high- burden countries that carry 80% of the global malaria burden (World Health Organisation, 2017). Malaria transmission in the country is high, stable and perennial with almost the entire population at risk (President's Malaria Initiative, 2017). Approximately 16 million cases and over 10,500 deaths are reported annually making malaria one of the most important diseases in the country (Ministry of Health, 2014). *P. falciparum* is the most dominant malaria species, and *A. gambiae s.s* is the commonest vector (Yeka et al., 2012). Since 2006, RBM has funded malaria control, prevention and treatment activities in Uganda up to the tune of US$600 mainly to support interventions scale-up (Talisuna et al., 2015).

1.4.1 Socioeconomic burden of malaria

Malaria is responsible for direct and indirect socio-economic costs to countries, households, and individuals (Gallup and Sachs, 2001). Countries with high malaria transmission are much more

poorer, have lower living standards and are less developed compared to countries with a lower transmission (Sachs and Malaney, 2002). At global level, over 56 million Disability Adjusted Lost Years (DALYs) are lost due to malaria annually (GBD 2016 DALYs and HALE Collaborators, 2017). Households in endemic countries incur high costs for meeting out-of-pocket payments for medical consultation fees, drugs, and transport to health facilities leading to substantial financial losses to families (Wang et al., 2005). At individual level, malaria results in lost productivity due to sickness, decreased school attendance due to absenteeism which impacts school performance and overall quality of life. This in turn impacts negatively on growth of industries and agriculture making the country unattractive to investors leading to a loss in investment and retarded socioeconomic development. In Uganda, it is estimated that households incur about $9 per bout of malaria equivalent to 3% of their annual income (Ministry of Health, 2014).

1.4.2 Malaria risk factors

Malaria risk is known to be influenced by several factors such as environmental/climatic (Siraj et al., 2014), interventions (O'Meara et al., 2010), socioeconomic (Protopopoff et al., 2009) and demographic factors (Graves et al., 2009).

1.4.2.1 Environmental/climatic factors

Malaria transmission is chiefly driven by environmental factors due to their influence of the development of malaria vectors and parasites (Thomson et al., 2017). Temperature determines the duration of parasite and larval development, as well as and vector survival (Tanser et al., 2003). Rainfall contributes to the formation of mosquito breeding sites, thus increasing vector populations (Thomson et al., 2017). Altitude is inversely related with temperature, and thus higher altitudes prolong stages of parasite development resulting in low transmission (Drakeley et al., 2005).

1.4.2.2 Interventions

The WHO recommended interventions of ITNs, IRS and ACTs have been shown to control and

prevent malaria in endemic settings due to their role in reducing human-vector contact, directly killing mosquitoes and lowering malaria parasite load in humans and populations at large (Bhattarai et al., 2007; Ceesay et al., 2008; Choi et al., 1995). ITNs, in particular, have shown the highest efficiency and cost-effectiveness in reducing malaria morbidity and mortality among children less than 5 years (Lengeler, 2004).

1.4.2.3 Socioeconomic factors

Malaria is a disease associated with low socio-economic development (Feachem and Sabot, 2008; Greenwood et al., 2008; Protopopoff et al., 2009; Tanner and de Savigny, 2008). This is because low socioeconomic status is directly linked to poverty which hinders affordability of adequate housing facilities and access to better health services which increases susceptibility to high malaria risk and/or transmission (Teklehaimanot and Mejia, 2008).

1.4.2.4 Demographic factors

The most important demographic factors that influence malaria risk are age and level of education. Young children have lower immunity which makes them highly susceptible to a higher malaria but the risk of malaria decreases with the development of immunity in older individuals (Pemberton-Ross et al., 2015). A higher level of education is closely linked with better socio-economic status, higher prevention awareness and the means to afford treatment measures (Noor et al., 2006).

1.5 Quantification of malaria risk

A number of measures are used to assess and compare the malaria burden and its transmission in different geographical settings and time periods including, Entomological Inoculation Rate (EIR), parasite prevalence (number of infected humans out of the total screened), and case incidence (number of newly infected humans) (Yé et al., 2009). The EIR is defined as the number of infective bites per person per night. However, for clinical malaria in endemic settings, parasite density and not prevalence is a better measure (Müller, 2011).

1.6 Malaria surveillance in Uganda

In Uganda, malaria surveillance is implemented through routine health facility data collection and reporting in the HMIS, and periodical execution of nationally representative household surveys, that is, Malaria Indicator Surveys (MIS) and Demographic Health Survey (DHS) (National Malaria Control Program, 2016). The national HMIS was established in the 1990s (Kintu et al., 2004). The system has undergone several upgrades including the most recent one of the adoption of the District Health Information Software System version 2 (DHIS2) in 2011 which involved transformation of a paper-based reporting and storage system to an electronic web-based system (Kiberu et al., 2014). Following this upgrade, data quality reporting, facility reporting and report timeliness have improved significantly. The Integrated Disease Surveillance and Response (IDSR) system used to monitor outbreaks of major diseases including malaria has been incorporated in the upgraded version.

RBM support in Uganda has been extended to the implementation of MIS and DHS surveys. The following surveys have been implemented since 2009; MIS 2009 and MIS 2014-15 (Uganda Bureau of Statistics and ICF International, 2015, 2010), and DHS 2011 and DHS 2016 (Uganda Bureau of Statistcs (UBOS) and ICF, 2017; Uganda Bureau of Statistics (UBOS) and ICF International Inc. 2012, 2012). These surveys facilitate the estimation of malaria prevalence in the country, identify the most affected population groups and high-burden areas, and track malaria interventions scale-up at national and subnational scale.

Also, since the inception of RBM in Uganda, two health facility assessment surveys have been conducted to evaluate facility readiness to provide basic healthcare services including malaria (Wane and Martin, 2013).

1.7 Major constraint to malaria surveillance in Uganda

The RBM support to malaria surveillance activities in Uganda has resulted in the availability of rich sources of routinely collected and survey data in the country. Despite this availability, data utilization remains low and the information extracted by NMCP is limited to national averages

that neither take into account subnational heterogeneities and disparities nor evaluate the effects of interventions on malaria burden changes in space and time. This is because the standard statistical methods are ill-suited for analysis of malaria surveillance data, yet MoH and NMCP lack the capacity to develop and apply the appropriate advanced methods. For instance, the usual statistical assumption of independence of data observations in standard statistical software does not hold for malaria surveillance data due to the presence of spatial and temporal correlation. Also, the analysis must take into account the fact that environmental factors' effects on malaria is not limited to one point in time but is distributed over time, as well as the strong seasonality trends originating from a high correlation between malaria and the environment, and the need to predict malaria risk at unsampled locations.

1.8 Bayesian spatio-temporal modeling and applications in malaria surveillance

Statistical modeling is used to determine important exposures for the outcome-exposure relationship and to predict the outcome at unobserved exposure values or future time. However, these models assume independence of observations, an assumption that is violated by malaria surveillance data due to the presence of spatial and temporal correlation arising out of similarity of exposures in neighboring areas, and proximal time points in time series data, respectively.

Bayesian spatio-temporal models are the state-of-the-art methods appropriate for analyzing geostatistical and spatio-temporal data. The models account for correlation of malaria data in space and time, by allowing extra parameters to be included as random effects for location and time. The spatial random effects are assumed to be latent data from an underlying Gaussian spatial process, and correlations between two locations are modeled as a function of the distance between them. On the other hand, temporal correlation can be adjusted by incorporating autoregressive terms in the models. The addition of these random effect results in a highly parameterized model making inference by maximum likelihood estimation unfeasible. However, this problem is easily handled by Bayesian inference via MCMC simulations (Gelfand and Smith, 1990). Since their first formulation by Diggle et al. (1998), these models have been

employed in mapping of malaria risk in Africa using contemporary and historical survey data to produce malaria risk maps for Mali (Gemperli et al., 2006b), West Africa (Gemperli et al., 2006a), Malawi (Kazembe et al., 2006), Botswana (Craig et al., 2007), Cote d'Ivoire (Raso et al., 2012), Kenya (Noor et al., 2009), Somalia (Noor et al., 2012), Nigeria (Adigun et al., 2015), Burkina Faso (Diboulo et al., 2016), Angola (Gosoniu et al., 2010), Tanzania (Gosoniu et al., 2012), Senegal (Giardina et al., 2012) and Zambia (Riedel et al., 2010). They have also been applied to model malaria incidence in Namibia (Alegana et al., 2013),Venezuela (Villalta et al., 2013), Mozambique (Zacarias and Andersson, 2011), Malawi (Kazembe, 2007), Zimbabwe (Mabaso et al., 2006), China (Clements et al., 2009), and in South Africa (Kleinschmidt et al., 2002).

The robustness of the Bayesian framework enables the extension of these models to capture complex features of malaria surveillance data including seasonality, changing risk profiles over time, and the distributed effect of the environment on malaria incidence. This flexibility is crucial for accurate estimation of malaria burden at national and subnational scales, prediction at unsampled locations, assessment of interventions and health system-related effects, and can be exploited in the development of forecasting models to support early warning system. This is crucial for improving malaria surveillance in Uganda and other settings with high endemicity. The results will inform priority setting, decision making, and guide timing and targeted deployment of interventions to maximize benefits so as to optimize resources to achieving the objectives in the UMRSP 2014-2020.

1.9 Thesis objectives

The main objective of this thesis was to develop Bayesian spatio-temporal models for malaria surveillance in Uganda.

1.9.1 Specific objectives

The specific objectives were to;

1) Assess the effects of interventions on the geographical distribution of malaria prevalence in the country
2) Determine the contribution of interventions on the spatio-temporal changes of parasitaemia risk
3) Estimate the effects of interventions on the space-time patterns of malaria incidence
4) Investigate interactions between climatic changes and intervention effects on malaria spatio-temporal dynamics
5) Assess the role of health facility readiness on severe malaria outcomes
6) Develop forecasting models to support a malaria early warning system in Uganda

Chapter 2: Geostatistical modeling of malaria indicator survey data to assess the effects of interventions on the geographical distribution of malaria prevalence in children less than 5 years in Uganda

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Abstract

Background

Malaria burden in Uganda has declined disproportionately among regions despite overall high intervention coverage across all regions. The Uganda Malaria Indicator Survey (MIS) 2014-15 was the second nationally representative survey conducted to provide estimates of malaria prevalence among children less than 5 years, and to track the progress of control interventions in the country. In this present study, 2014-15 MIS data were analyzed to assess intervention effects on malaria prevalence in Uganda among children less than 5 years, assess intervention effects at the regional level, and estimate geographical distribution of malaria prevalence in the country.

Methods

Bayesian geostatistical models with spatially varying coefficients were used to determine the effect of interventions on malaria prevalence at national and regional levels. The spike-and-slab variable selection was used to identify the most important predictors and forms. Bayesian kriging was used to predict malaria prevalence at unsampled locations.

Results

Indoor Residual Spraying (IRS) and Insecticide Treated Nets (ITN) ownership had a significant but varying protective effect on malaria prevalence. However, no effect was observed for Artemisinin Combination-based Therapies (ACTs). Environmental factors, namely, land cover, rainfall, day and night land surface temperature, and area type were significantly associated with malaria prevalence. Malaria prevalence was higher in rural areas, increased with the child's age, and decreased with higher household socioeconomic status and a higher level of mother's education. The highest prevalence of malaria in children less than 5 years was predicted for regions of East Central, North East, and West Nile, whereas the lowest was predicted in Kampala and South Western regions, and in the mountainous areas in Mid-Western and Mid-Eastern regions.

Conclusion

IRS and ITN ownership are important interventions against malaria prevalence in children less than 5 years in Uganda. The varying effects of the interventions call for the selective implementation of control tools suitable to regional ecological settings. To further reduce malaria burden and sustain malaria control in Uganda, current tools should be supplemented by health system strengthening and socio-economic development.

Key words: Indoor residual spraying, artemisinin combination-based therapies, insecticide treated nets, Bayesian geostatistical modeling, spatially varying coefficient, kriging, malaria prevalence, malaria indicator survey

2.1 Introduction

Malaria remains one of the leading public health burdens in the world despite the remarkable achievements made towards its control and prevention since the beginning of the second millennium. Recent global estimates indicate that malaria is responsible for over 214 million cases and over 438,000 deaths (World Health Organization, 2015a). Most of this burden is concentrated in Sub-Saharan Africa (SSA) region which accounts for 90% of the mortality burden, most of which occur among children less than 5 years old (World Health Organization, 2015a). However, malaria has gone down from first to the fourth highest cause of mortality in this age group during the last 15 years (World Health Organization, 2015a).

Uganda has the fourth highest number of *Plasmodium falciparum* infections (World Health Organization, 2015a) and some of the highest reported malaria transmission rates in the world (Talisuna et al., 2015). Ninety-five percent of the country has stable malaria transmission, with the rest having a low and unstable transmission with potential for epidemics. Malaria is responsible for 33% of all outpatient visits and 30% of hospital admissions (National Malaria Control Program, 2016). Ninety-nine percent of malaria cases are attributed to *P. falciparum* species - *Anopheles gambiae s.1* and *An. funestus* being the most common vectors (Yeka et al., 2012).

Vector control tools, that is, Insecticide Treated Nets (ITNs), Indoor Residual Spraying (IRS), and case management with Artemisinin-based Combination Therapies (ACTs) are at the forefront of malaria control and prevention in Uganda (National Malaria Control Program, 2016). Malaria Indicator Surveys (MIS) are nationally representative surveys conducted every 5 years to estimate malaria prevalence among children of age less than 5 years and track the progress of coverage of control interventions. The most recent MIS conducted in Uganda showed that overall prevalence of malaria among children age less than 5 years was 19.0% (Uganda Bureau of Statistics and ICF International, 2015). Results also indicated that coverage of interventions was

high across all regions. However, there were wide variations in regional malaria prevalence, varying from less than 5% in Kampala and South Western regions to over 25% in East Central, North East and, West Nile regions (Uganda Bureau of Statistics and ICF International, 2015). Whether the differences in the prevalence are due to variations in climatic, socio-economic, and demographic characteristics, or as a result of intervention effects varying in space needs to be investigated empirically.

MIS have been used to analyze the effect of interventions on malaria prevalence using both non-spatial and Bayesian geostatistical methods. The latter give reliable estimates because they take into account correlation of malaria prevalence in space arising from common exposures affecting neighboring areas similarly. Bayesian geostatistical models have been used in mapping of malaria burden (Gething et al., 2011) and recently in the analysis of MIS data in high endemic countries of SSA, namely, Zambia (Riedel et al., 2010), Angola (Gosoniu et al., 2010), Tanzania (Gosoniu et al., 2012), Senegal (Giardina et al., 2012), Nigeria (Adigun et al., 2015) and Burkina Faso (Diboulo et al., 2016). Despite comparable malaria transmission intensities in these countries, findings showed varied effects of interventions on malaria prevalence among children less than 5 years. For instance, a protective and non-protective effects were reported for ITNs and IRS respectively in Zambia (Riedel et al., 2010), Angola (Gosoniu et al., 2010) and Senegal (Giardina et al., 2012). On the other hand, no effects were observed for the role of interventions in Nigeria (Adigun et al., 2015), and Tanzania (Gosoniu et al., 2012). In Liberia (Giardina et al., 2014) and Burkina Faso (Diboulo et al., 2016), intervention effects were protective at sub-national level but had no effect at the country level.

In the current study, we analyzed the Uganda MIS 2014-15 using Bayesian geostatistical models to: i) determine the effect of interventions on malaria prevalence in children less than 5 years adjusted for environmental, demographic and socio-economic characteristics, ii) assess intervention effects at regional level, and iii) obtain spatially explicit estimates of malaria

prevalence in this age group. A malaria risk map is a vital tool for efficient planning, resource mobilization, monitoring, and evaluation. To date, the only map available for Uganda is the one extracted from the new world malaria map (Gething et al., 2011) which is now out-dated since it does not take into account contemporary effects of interventions, socio-economic status, and climatic/environmental conditions.

2.2 Methods

2.2.1 Country profile

Uganda is a landlocked country located in East Africa and shares borders with South Sudan to the north, Kenya to the east, the Democratic Republic of Congo to the west, and Tanzania and Rwanda to the south. It lies between latitudes 1^0 south and 4^0 north of the equator, with altitude ranging from 620 m to 5,111 m above sea level, and mean annual temperatures between 14^0C and 32^0C. It has two rainfall seasons in a year, a shorter one during March to May and a longer season spanning September to December. A range of ecosystems covers the country with the south dominated by tropical rain forests which gradually turn into savannah woodland and semi-desert in the north. The country is divided into 112 districts grouped into 10 regions and covers an area of about 241,039 square kilometres.

Uganda has a population of 35 million people living in 7.3 million households (Uganda Bureau of Statistics, 2016). The population is largely young with 50% of the population constituted with individuals of age 0-15 years. The proportion of the population of children age less than 5 years is 17.7% (Uganda Bureau of Statistics, 2016).

2.2.2 Uganda MIS 2014-15

The 2014-15 MIS was based on a stratified two-stage cluster design (Uganda Bureau of Statistics and ICF International, 2015). In the first stage, 20 sampling strata were created and 210 clusters were selected with probability-proportional-to-size sampling. At the second stage, using

complete lists of households in the selected clusters, 28 households were chosen from each cluster with equal probability systematic sampling.

All women of age 15-49 years in the sampled households, who were either permanent residents or visitors in the household on the night preceding the survey, were eligible for interview. Similarly, all children of age less than 5 years were eligible for malaria testing.

Blood samples were taken from fingers or heels of children age less than 5 years and tested on-spot using Rapid Diagnostic Tests (RDTs). In addition, thick and thin blood smears were prepared and tested by microscopy. Results were recorded as either positive or negative if malaria parasites were found or not in the blood sample, respectively. In this study, microscopy results were considered because of the reduced sensitivity of RDTs in populations that have recently been treated and cleared of malaria parasites due to the presence of the residual HRP2 antigen (World Health Organization and others, 2015).

2.2.3 Ethical approval

In this study, we used secondary data that was made available by the Uganda Bureau of Statistics (UBOS) and the Demographic Health Survey (DHS) MEASURE group based in the United States of America. According to survey protocols and related documents (Uganda Bureau of Statistics and ICF International, 2015), the ethical approval process was described as follows; The Institutional Review Board of International Consulting Firm (ICF) of Calverton, Maryland, USA reviewed and approved the Uganda MIS 2014-15. This complied with the United States Department of Health and Human Services requirements for the "Protection of Human Subjects" (45 CFR (Code of Federal regulations) 46).
The survey was also reviewed and approved by Makerere University School of Biomedical Sciences Higher Degrees Research and Ethics committee (SBS-HDREC), and the Uganda National Council for Science and Technology (UNCST).

An interview was conducted only if the respondent provided their verbal consent in response to being read an informed consent statement by the interviewer. Also, verbal informed consent for each parasitaemia test was provided by the child's parent/guardian/caregiver on behalf of children less than 5 years before the test was conducted. Verbal consent was conducted by the interviewer reading a prescribed statement to the respondent and recording in the questionnaire whether or not the respondent consented or assent was provided. The interviewer signed his or her name attesting to the fact that he/she read the consent statement to the respondent. Verbal consent was preferred over written consent because of low literacy levels especially in rural areas of Uganda (Uganda Bureau of Statistics and ICF International, 2015).

2.2.4 Predictor variables

Malaria transmission is known to be influenced by several factors including interventions (O'Meara et al., 2010), environmental/climatic (Siraj et al., 2014), socio-economic (Protopopoff et al., 2009) and demographic factors (Graves et al., 2009). Environmental/climatic proxy variables were extracted from remote sensing sources for the period February 2014 – January 2015 (Table 2.1). Demographic variables were captured on survey tools, namely, the age of the child, residential location of the household, and mother's highest level of education.

Data on control interventions were captured on survey questionnaires including ownership and use of ITNs, ACT use, and IRS. The data on IRS coverage were collected at the household level, whereas that of ITN and ACT use was collected for each child in the selected household. Intervention coverage indicators were generated following standard definitions of Roll Back Malaria (World Health Organisation, 2013). The ITN ownership indicators generated and used in the study were; the proportion of households with at least one ITN (pro_1ITN), the proportion of households with one ITN for every two people (pro_1ITN4two), and proportion of the population with access to an ITN within their household (pro_itnaccess). ITN use indicators were; the proportion of children less than 5 years who slept under an ITN on the night preceding

the survey (pro_slept5itn), the proportion of the population that slept under an ITN in the night preceding the survey (pro_sleptitn), and proportion of ITNs used last night preceding the survey (pro_itnused).

ACT coverage was measured as the proportion of fevers reported in the last 2 weeks before the survey that was treated with any ACTs. The indicator on IRS coverage was derived as the proportion of households sprayed in the last six months.

The wealth index available in the data and calculated as a weighted sum of household assets using principal component analysis (Rutstein and Johnson, 2004) was used a proxy for socioeconomic status.

Prior to Bayesian model fitting, collinearity between all pairs of independent variables was assessed using non-spatial regression methods based on values of Variance Inflation Factor (VIF) and Tolerance Values (TR).

Table 2.1: Sources, spatial and temporal resolution of environmental/climatic and population data

Data	Source	Period	Spatial resolution	Temporal resolution
Annual average Day and Night Land Surface Temperature (LST)	MODIS	February 2014- January 2015	1x1km^2	8 days
Annual average Normalized Difference Vegetation Index (NDVI)	MODIS	February 2014- January 2015	1x1km^2	16 days
Population data	Worldpop	2014	0.1x0.1km^2	na
Annual average Rainfall	U.S. Geological Survey-Earth Resources Observation Systems (USGSS)	February 2014- January 2015	8x8km^2	10 days
Altitude (Digital Elevation Model)	Shuttle Radar Topographic Mission (SRTM)	2000	0.5x0.5km^2	na
Water bodies	MODIS	-	0.5x0.5km^2	na
Urban Rural extent	Global Rural and Urban Mapping project	February 2014- January 2015	1x1km^2	na

MODIS: Moderate Resolution Imaging Spectroradiometer
na: Not applicable

2.2.5 Bayesian geostatistical modeling

Three Bayesian geostatistical logistic regression models were fitted to determine the geographical distribution of malaria prevalence in children less than 5 years in Uganda, assess the adjusted effect of interventions on malaria prevalence, and estimate the effects of

interventions at the regional level. The first model included only environmental predictors, the second comprised of environmental, demographic, and socio-economic factors, whereas the third was modeled with spatially varying coefficients for interventions adjusted for the effect of environmental, socioeconomic status and demographic predictors. The third model assesses the effects of interventions at the regional level using spatially varying coefficients (Giardina et al., 2014) and is formulated assuming a conditional autoregressive (CAR) prior distribution (Cressie, 2015) which introduces a neighbor-based spatial structure for the regression coefficients for each intervention effect (Bivand et al., 2013). Neighbors were defined as the adjacent areas of each region. This model was adjusted for the effect of environmental/climatic, socio-economic status and demographic factors.

The outcome of interest was the parasitaemia test result of a child tested in a sampled household. To adjust for spatial correlation present in malaria data due to similar exposure effect in neighboring areas, cluster-specific random effects were added to each model. The cluster random effects were assumed to arise from a Gaussian stationary process with a covariance matrix capturing correlation between any pair of cluster locations as a function of their distances.

To improve model fit and parameter estimation, a Bayesian geostatistical variable selection was used to select the most important predictors and form in explaining variation in malaria prevalence for the three models mentioned above. In model 1, selection consisted of introducing an indicator variable for every climatic predictor and estimating the probabilities of excluding or including the predictor into the model in linear or categorical form. These probabilities indicate the proportion of models including a given predictor out of models generated from all combinations of predictors. Variables were categorized using predictor quartiles. Only variables with an inclusion probability of more than 50% were used to predict malaria prevalence in children less than 5 years at unsampled locations.

Similarly, in the second model, a geostatistical variable selection was performed to choose the most important intervention, socio-economic and demographic predictors for malaria prevalence. This model was adjusted for the effect of environmental predictors fitted in model 1. The indicator with the highest probability of inclusion per group of ITN ownership (pro_1ITN, pro_1ITN4two, pro_itnaccess) and ITN use (pro_slept5itn, pro_sleptitn, pro_itnused) was selected.

Prediction of malaria prevalence was performed using Bayesian kriging (Diggle and Giorgi, 2016) over a regular grid of 52,495 pixels at 4 km^2 resolution covering the entire country.

The population-adjusted number of individuals infected with malaria was estimated by first combining the high spatial resolution population data obtained from worldpop (Worldpop dataset download, 2016) with the predicted pixel-level malaria prevalence estimates. The population data were re-scaled from their initial 100x100m spatial resolution to the 2x2km resolution of the gridded risk estimates. The number of children less than 5 years infected with malaria per pixel was estimated by multiplying population counts by a factor of 17.7% - the proportion of the population under 5 years (Uganda Bureau of Statistics, 2016). The pixel-level estimates were aggregated at the regional level to produce number infected per region.

Data analysis was carried out in STATA (StataCorp. 2015. *Stata Statistical Software: Release 14*. College Station, TX: StataCorp LP). OpenBUGS version 3.2.3 (Lunn et al., 2000) was used to implement the variable selection approach and to perform model fit. The Bayesian kriging was implemented using a program written by the authors in R statistical computing and graphics software ("R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL http://www.R-project.org/," 2014). Maps were produced using ESRI's ArcGIS 10.2.1 for Desktop (http://www.esri.com/).

Parameter estimates were summarized using posterior medians and the corresponding 95% Bayesian Credible Intervals (BCI). Model estimates were exponentiated to produce Odds

Ratios (OR). The effect of a predictor was considered to be important if the 95%BCI of the coefficient did not include a zero. The details of the fitted models are given in the Appendix.

2.3 Results

A total of 4939 children age 0-59 months were tested for malaria from 210 clusters. The overall prevalence of malaria by microscopy was 19.0%. However, in this study, we used data from only 193(91.9%) clusters whose geo-referenced information was available at the time of analysis (Fig 1). This reduced sample had 4591 children tested for malaria with malaria prevalence of 19.5% which varied from 0% in Kampala region to over 38.0% in East Central region. Table 2 shows the overall and regional coverage distribution of intervention indicators.

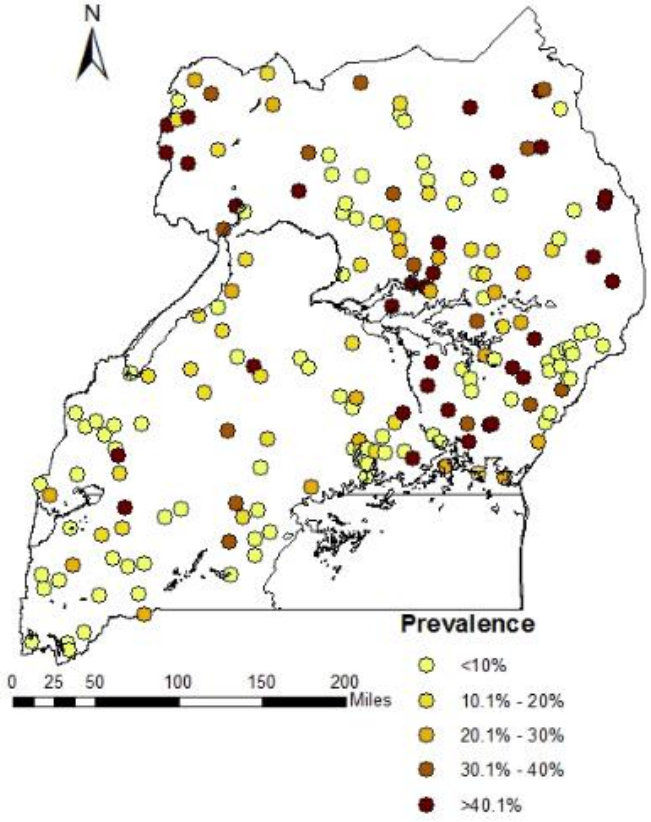

Figure 2.1: Observed malaria prevalence at survey locations in Uganda, MIS 2014-15

Nine out of every ten households had an ITN, but the proportion of households having one ITN for every two people was lower, varying from 36.3% in East Central to almost 70% in South Western region. At the country level, 80% of the population had access to an ITN in their households, with coverage ranging from 67% in East Central region to over 90% in South

Western region. Seventy-five percent of the population slept under an ITN on the night preceding the survey. Comparing ITN assess and ITN use shows a surplus of 5% unused ITNs.

Three out of every four children of age less than 5 years slept under an ITN - the lowest coverage was observed in Central 1 region, while the highest was reported in North East region.

Case management using ACTs ranged from 60% in Kampala to almost 80% in East Central region.

About one out of every ten households in the country had been sprayed in the last 6 months, but this intervention was mainly implemented in the Mid-North region where almost 6 out of every 10 households were sprayed.

Table 2.2: Coverage of control interventions by region

Region	Number of Clusters	Prevalence	pro_1ITN[a]	pro_1ITN4two[b]	pro_slept5itn[c]	IRS[d]	ACT[e]	pro_itnaccess[f]	pro_sleptitn[g]
North East	32	32.3	0.96	0.51	0.86	0.02	0.71	0.80	0.84
West Nile	16	27.4	0.96	0.64	0.76	0.02	0.65	0.86	0.79
Mid-North	31	14.8	0.94	0.54	0.77	0.55	0.71.	0.82	0.77
Mid-Western	14	14.1	0.96	0.52	0.83	0.0	0.64	0.81	0.80
Mid-Eastern	24	14.1	0.97	0.52	0.81	0.0	0.79	0.82	0.76
East Central	15	38.6	0.86	0.36	0.69	0.0	0.72	0.67	0.66
Central 2	17	20.4	0.89	0.46	0.66	0.0	0.72	0.73	0.66
Central 1	17	11.2	0.87	0.51	0.65	0.02.	0.60	0.74	0.62
South Western	11	4.5	1.00	0.69	0.66	0.0	0.60	0.91	0.67
Kampala	16	0.0	0.94	0.62	0.71	0.03	0.57	0.82	0.77
Overall	193	19.5	0.94	0.54	0.76	0.1	0.68	0.81	0.75

[a]Proportion of households with at least one ITN
[b]Proportion of households with at least one ITN for every two people
[c]Proportion of children less than 5 years who slept under an ITN
[d]Proportion of households sprayed in the last 6 months
[e]Proportion of fevers treated with any ACTs
[f]Proportion of population who had access to an ITN
[g]Proportion of population who slept under an ITN

In Table 2.3, results from the Bayesian geostatistical variable selection are presented. In model 1, day LST (categorical), night LST (linear), land cover and area type were selected. These selected variables were used for predicting malaria prevalence in children less than 5 years at unsampled locations. Results in model 2 indicate a high probability of inclusion (>90%) for IRS, wealth index, age and mother's highest level of education. However, indicators for ITN and

ACTs were selected with low probabilities which might be indicative of a weak relationship with malaria prevalence.

Table 2.3: Posterior inclusion probabilities for environmental, intervention, socio-economic and demographic factors

Variable	Posterior inclusion probability (%)	
	Model 1†	Model 2††
Land surface temperature (day)	0.0	0.0
Land surface temperature (night)	87.6	74.1
Normalized difference vegetation index	41.9	36.2
Rainfall	4.6	26.9
Altitude	12.6	27.2
Distance to water bodies	0.0	14.1
Land cover	100	100
Land surface temperature (day)*	100	100
Land surface temperature (night)*	0.0	0.0
Normalized difference vegetation index*	0.0	0.0
Rainfall *	0.0	0.0
Altitude *	0.0	0.0
Distance to water bodies*	0.0	0.0
Area type (rural vs urban)*	100	100
Intervention		
IRS use		100
ITN ownership		
pro_1ITN4two		8.3
pro_1ITN		2.3
pro_itnaccess		27.4
ITN use		
pro_slept5itn		14.3
pro_sleptitn		0.0
pro_itnused		17.6
Case management of malaria at health facilities		
Proportion of fevers treated with any anti-malarial		12.9
Proportion of fevers treated with ACTs		53.6
Socioeconomic status, demographic		
Wealth index		100
Area type		93.7
Age		100
Mother's highest level of education		94.4

* Categorical form
†Only climatic predictors
††Intervention + climatic + SES + demographic

Table 2.4 presents results from Bayesian geostatistical models. In model 1 results show that day LST, night LST, land cover, and area type was significantly associated with malaria prevalence. Also, increases in day and night LST were significantly associated with higher odds

of malaria prevalence. Moreover, the odds of malaria prevalence were more than two times higher in cropping areas compared to forested areas (OR=2.12 95% BCI: 1.25-2.29).

The adjusted effects of interventions on malaria prevalence are shown in model 2. The odds of malaria in children who lived in households that had been sprayed were 78% less than those living in unsprayed houses (95% BCI: 58%-86%). ITN access was associated with decreased odds of malaria prevalence. However, results show a risk factor effect for ITN use and no effect for ACTs use.

A decreasing trend of malaria odds with increasing wealth quintile was observed. Malaria odds were 48% (95% BCI: 39%-58%) and 81% (95% BCI: 73%-86%) lower for richer and richest wealth quintile respectively compared to the poorest quintile.

Rural areas had more than two times the prevalence of malaria compared to urban areas (OR=2.06 95% BCI: 1.96-2.19).

The prevalence of malaria increased with age of a child reaching almost 5 times higher in children age 49-59 months compared to children age <=12 months (OR=4.77 95% BCI: 4.47-5.97).

A decreasing trend of malaria prevalence was observed with mother's highest level of education. Malaria prevalence was 15% (95% BCI: 11-26%) and 43% (95%BCI: 33- 43%) lower in children whose mothers had attained primary and post-primary education compared to children whose mothers had no education respectively.

Also, results indicate a strong spatial correlation of malaria prevalence of up to 47.7km (Range: 40.7-56.4).

In Table 2.5 results from the spatially varying coefficient model are presented and indicate that intervention effects varied by region. The effect of ITN ownership was protective in the regions of North East, West Nile and South Western, whereas that of ITN use was protective in Mid-Western. ACT use was protective in Mid-western, North East, and West Nile regions.

Table 2.4: Posterior estimates for the effect of environmental, intervention, socio-economic factors

Variable	Parasitaemia prevalence (%)	Model 1†	Model 2††
		OR (95% BCI)	OR (95% BCI)
Land cover			
Forest	17.8	1.0	1.0
Crops	27.2	2.12 (1.25, 2.29)*	1.35 (1.17, 1.42)*
Others	10.0	0.56 (0.39, 0.73)*	0.59 (0.44, 0.71)*
Land surface temperature (Day)			
<=31.4	11.7	1.0	1.0
31.4-33.8	19.7	1.98 (1.69, 2.52)*	2.87 (2.42, 3.08)*
>=33.8	26.6	3.19 (2.83, 3.85)*	1.98 (1.68, 2.01)*
Land surface temperature (Night)	-	1.75 (1.64, 1.82)*	1.25 (1.17, 1.26)*
Area type			
Urban	6.0	1.0	1.0
Rural	21.6	6.25 (5.62, 8.60)*	2.06 (1.96, 2.19)*
Wealth Index			
Poorest	27.7		1.0
Poorer	21.1		0.86 (0.72, 1.04)
Middle	20.8		0.77 (0.85, 1.15)
Richer	11.9		0.52 (0.42, 0.61)*
Richest	3.3		0.19 (0.14, 0.27)*
ITN ownership			
Proportion of population with access to an ITN in their households			0.78 (0.67, 0.89)*
ITN use			
Proportion of ITNs used the previous night			1.68 (1.52, 1.77)*
Indoor Residual Spraying			
Not sprayed	21.0		1.0
Sprayed	5.0		0.22 (0.14, 0.42)*
Case management			
Proportion of fevers treated with ACTs			1.29 (1.00, 1.38)
Age (months)			
<=12	9.6		1.0
13-24	16.1		2.16 (1.85, 2.41)*
25-36	22.5		3.67 (3.08, 4.16)*
37-48	23.1		3.54 (2.83, 3.83)*
49-59	26.0		4.77 (4.47, 5.97)*
Mother's education			
None	26.4		1.0
Primary	17.8		0.85 (0.74, 0.89)*
Post primary	8.2		0.57 (0.57, 0.67)*
Variances			
Gaussian process		0.45 (0.40, 0.48)	0.77 (0.62, 0.80)
Range (km)		52.2 (33.9, 69.5)	47.7 (40.7, 56.4)

†Only climatic factors

††Intervention + climatic + SES + demographic

*Statistically important

Table 2.5: Posterior median and 95% credible intervals for spatially varying effect of interventions on malaria prevalence

Region	**ITN Ownership**	**ITN Use**	**ACTs**
	OR (95% BCI)	**OR (95% BCI)**	**OR (95% BCI)**
Central 1	0.93 (0.69, 1.28)	1.58 (0.85, 1.72)	1.75 (1.42, 2.40)
Central 2	0.93 (0.70, 1.53)	1.09 (0.73, 2.44)	1.52 (1.19, 1.90)
East central	1.50 (0.77, 1.86)	0.94 (0.63, 1.11)	2.11 (1.69, 4.25)
Kampala	1.17 (0.38, 1.25)	1.44 (0.28, 2.26)	1.03 (0.22, 1.67)
Mid-North	1.16 (0.93, 1.41)	0.92 (0.58, 1.38)	0.36 (0.21, 0.71)*
Mid-western	1.02 (0.84, 1.73)	0.92 (0.75, 0.98)*	0.91 (0.85, 1.21)
Mid-eastern	1.09 (1.00, 1.50)	1.13 (0.91, 1.33)	1.39 (0.90, 2.30)
North East	0.85 (0.73, 0.94)*	0.93 (0.66, 1.09)	0.61 (0.46, 0.68)*
South Western	0.87 (0.50, 0.98)*	0.98 (0.77, 2.06)	1.85 (1.07, 2.19)
West Nile	1.44 (1.14, 1.51)	1.01 (0.68, 1.43)	0.45 (0.41, 0.67)*
Variance	**Median (95% BCI)**	**Median (95% BCI)**	**Median (95% BCI)**
Spatially varying	3.27 (1.60, 3.92)	2.97 (1.73, 7.61)	1.01 (0.66, 3.22)

*Statistically important and protective

Fig 2.2 shows maps of the predicted median malaria prevalence, the 2.5th and 97.5th percentiles of the posterior predictive distribution. Malaria prevalence varied from as low as 0.03% to 77.0% with a median of 17.4%. A high prevalence (>20.0%) was predicted for regions of East Central, North East, and West Nile, while low prevalence (<5.0%) was predicted for Kampala and South Western regions. More so, a low prevalence was predicted for mountainous areas of Rwenzori and Elgon located in the Mid-Western and Mid-Eastern regions, respectively.

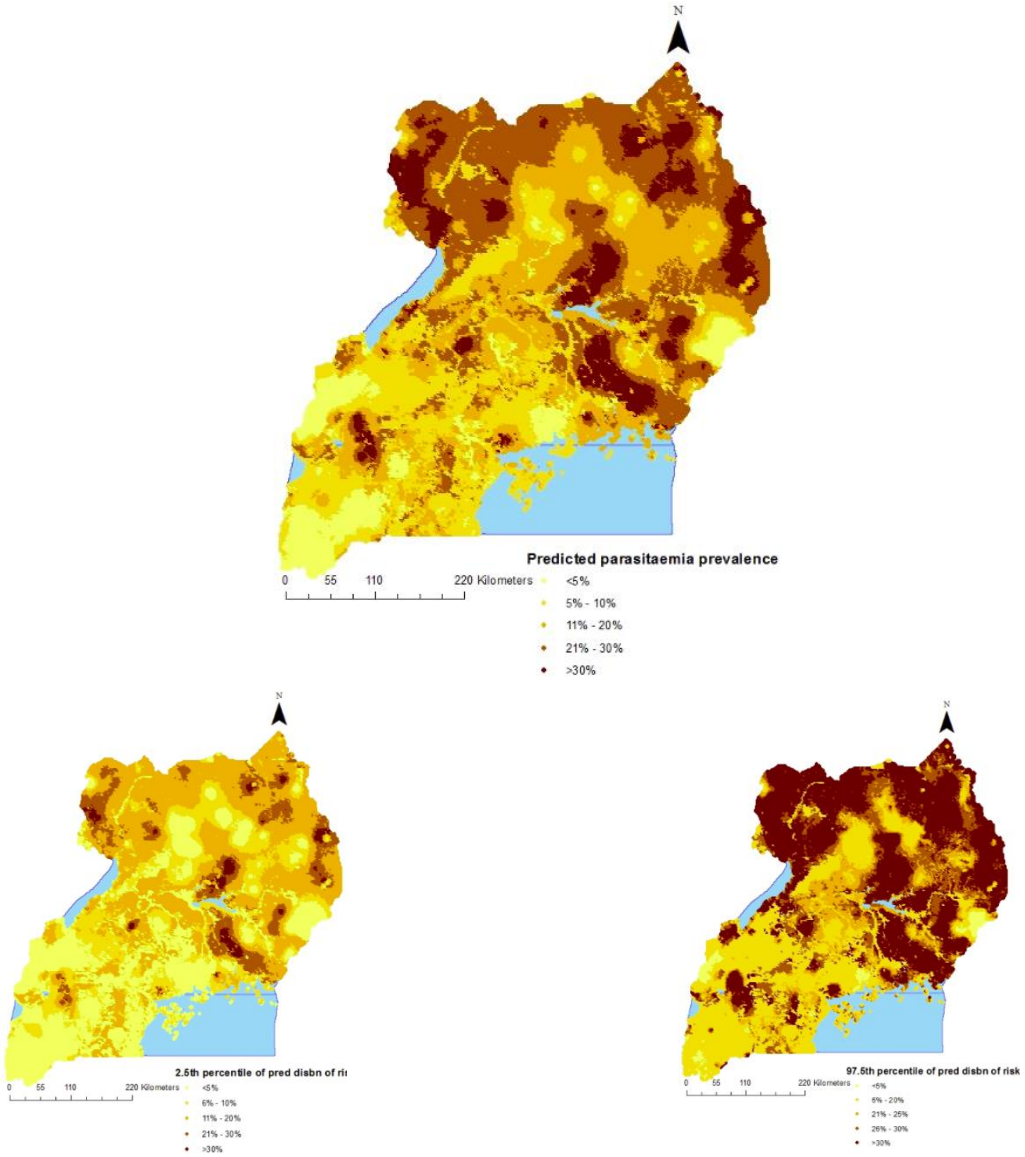

Figure 2.2: Predicted malaria prevalence in children less than 5 years; median (top), 2.5th percentile (bottom left) and 97.5th percentile posterior predictive distribution (bottom right)

The estimated number of children less than 5 years infected with malaria and the population adjusted prevalence are shown in Table 2.6. The distribution of infected children in the country is presented in Fig 2.3.

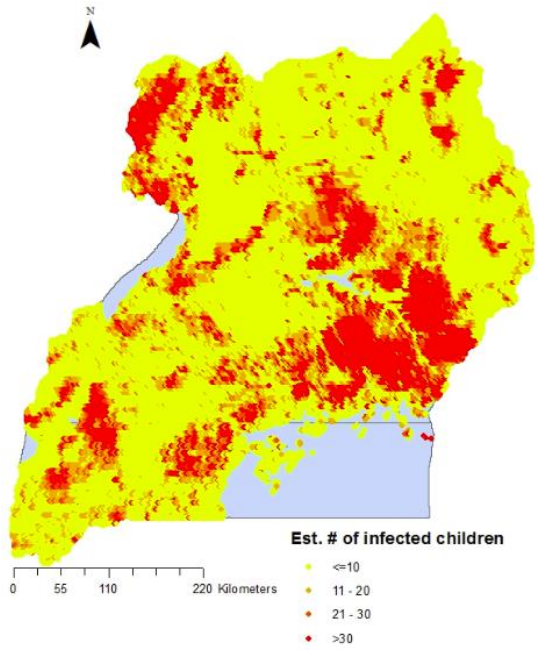

Figure 2.3: Estimated number of children less than 5 years infected with malaria

A total of 825,636 (812,316-839,958) children were estimated to have malaria in 2014. The regions with the highest estimated number of infected children were; East Central, North East, and West Nile. Kampala region had the lowest number of infected children. Population-adjusted prevalence was 17.6% (95%BCI 17.1%, 17.7%), and varied from 0.9% in Kampala to 26.0% in West Nile. The map shows the highest concentration of infected children in East Central.

Table 2.6: Estimated number of infected children less than 5 years and population-adjusted prevalence

Region	Observed prevalence (n/N)	Population of under 5 children	Estimated number of infected children n (95%BCI)	Population adjusted estimated prevalence % (95%BCI)
North East	32.3 (277/857)	479,691	119,871 (119,872, 125,485)	23.3 (23.1, 23.4)
West Nile	27.4 (116/423)	414,062	106,377 (100,986, 111769)	25.8 (25.5, 26.0)
Mid-North	14.8 (111/748)	515,113	98,846 (95,745, 101,948)	20.0 (19.8, 20.2)
Mid-Western	14.1 (68/482)	660,687	77,027 (74,023, 80,032)	12.9 (12.7, 13.1)
Mid-Eastern	14.1 (70/498)	524,051	79,734 (76,270, 83,200)	16.8 (16.4, 17.2)
East Central	38.6 (125/324)	516,382	138,191 (132,283, 144,100)	25.3 (24.8, 25.8)
Central 2	20.4 (76/373)	596,969	87,562 (83,516, 91,609)	14.4 (14.2, 14.6)
Central 1	11.2 (34/305)	652,194	58,314 (56,819, 59,208)	10.6 (10.4, 10.8)
South Western	4.5 (19/425)	752,314	56,819 (55,958, 60,671)	8.8 (8.6, 9.1)
Kampala	0.0 (0/156)	357,783	2,895 (2313, 3479)	0.9 (0.8, 1.1)
Overall	19.5 (896/4591)	5,469,245	825,636 (812,316, 838,958)	17.6 (17.1, 17.7)

2.4 Discussion

In this study, we analyzed the Uganda 2014-15 MIS data using Bayesian geostatistical models to determine the effect of interventions on the geographical distribution of malaria prevalence in children less than 5 years in Uganda and its regions and obtained spatially explicit estimates of malaria prevalence burden in this high-risk age group. Indicator variables pertaining to the coverage of interventions of IRS, ITNs, and ACTs were calculated from the data using standard definitions (World Health Organisation, 2013).

Bayesian geostatistical models fitted via Markov Chain Monte Carlo simulation methods were used to determine the adjusted effect of interventions on malaria prevalence. A geostatistical variable selection was used to choose the most important predictors for explaining variation in malaria prevalence, and their best functional form to improve model predictive ability and efficiency in parameter estimation.

Land cover, day LST, night LST, and area type were the most important environmental/climatic factors. These variables were among the list of climatic factors compiled in a systematic audit by Weiss et al, 2015 (Weiss et al., 2015) as important for malaria mapping. Also, these findings are similar to results reported from analyses of MIS data in Nigeria (Adigun et al., 2015) and Burkina Faso (Diboulo et al., 2016).

IRS and ITN ownership had a protective effect against malaria prevalence. Similar results were reported by Roberts and Matthews (2016) (Roberts and Matthews, 2016) who analysed the Uganda MIS 2014-15 data using a classical generalized linear model. The observed strong effect of IRS may be attributed to its effectiveness in killing adult mosquitos as they rest on walls after feeding which cuts short their development cycle and thus reduce vector density resulting in decreased malaria transmission intensity (WHO, 2006). However, IRS coverage was low in the country with the exception of the Mid-North region where this intervention implemented in 10 districts. Bukirwa et al., (2009) (Bukirwa et al., 2009) have attributed significant reduction of

malaria prevalence, morbidity and mortality in this region to IRS intervention. In other regions, IRS coverage is still very low (Uganda Bureau of Statistics and ICF International, 2015). The low coverage of this intervention has also been reported in other high endemic countries, namely, Tanzania (Gosoniu et al., 2012), Burkina Faso (Diboulo et al., 2016), Senegal (Giardina et al., 2012), Angola and Mozambique (Giardina et al., 2014). This could be attributed to the negative campaign against the use of DDT (Munguambe et al., 2011).

The protective effect of ITN ownership has been demonstrated in other studies (Giardina et al., 2014; Gosoniu et al., 2010; Lengeler, 2004). However, the observed lower effect of ITNs compared to IRS is inconsistent with results from other studies which showed that ITNs are a more effective and cost-effective tool (Fullman et al., 2013).

Unexpectedly, study results showed an increase in malaria prevalence with ITN use. This finding contradicts findings from other studies that have reported ITN efficacy (Choi et al., 1995; Lengeler, 2004; ter Kuile et al., 2003) and effectiveness (Dhimal et al., 2014; O'Meara et al., 2010; Snow and Marsh, 2010). However, these results are consistent to recent findings for Burkina Faso (Diboulo et al., 2016), Nigeria (Adigun et al., 2015), Tanzania (Gosoniu et al., 2012), and Senegal (Giardina et al., 2012). The lack of protective effect for high ITN use coverage could be attributed to human behaviour such as sleeping patterns where the population tends to stay longer outdoors at night (Stevenson et al., 2012), inconsistent ITN use especially during the dry season (Atieli et al., 2011), incorrect use and/or use of worn out ITNs (Githinji et al., 2010), the emerging pyrethroid resistance to insecticides in Uganda (Morgan et al., 2010; Ramphul et al., 2009; Verhaeghen et al., 2010), and high ITN use in areas of high malaria transmission.

Furthermore, results showed a lack of effect of ACTs on malaria prevalence unlike in other studies that demonstrated that ACTs were associated with a reduction in malaria transmission and risk (Bhatt et al., 2015a; Mehta and Pandit, 2016). However, this finding

should be interpreted cautiously because the data for this intervention was based on reported fevers which had been treated with any ACTs. This unexpected finding may be due to the fact that data for this intervention was based on reported fevers which had been treated with any ACTs. However, no data was available to confirm whether the reported fevers were malaria-related or not (Uganda Bureau of Statistics and ICF International, 2015), yet fevers in young children can be caused by several illnesses other than malaria (D'Acremont et al., 2014). A similar finding was reported in the Burkina Faso MIS study (Diboulo et al., 2016).

Environmental conditions were important predictors of malaria prevalence. This finding further augments the evidence that the environment is a key driver of malaria transmission (Reiner et al., 2015). Increases in day and night LST were associated with a high malaria prevalence. This relationship can be attributed to the fact that warmer temperatures accelerate larva stages of mosquito lifecycle (Gullan and Cranston, 2014). Other studies have also arrived at the same conclusion (Koita et al., 2012).

Areas where crops were grown had a higher risk of infection compared to forested areas which may indicate the agricultural transformation effect on the ecological landscape which results in the creation of suitable breeding habitats for mosquitoes. Similar results have been reported by Munga et al., (2016) (Munga et al., 2006).

Living in rural areas was associated with a higher burden of malaria prevalence compared to urban areas. This may be due to the fact that rural areas in Uganda are characterized with inadequate health services and poor housing conditions which predispose individuals to higher malaria prevalence (Ministry of Finance, 2014; Yeka, 2012).

Furthermore, older children were at a higher risk of being infected with malaria compared to infants. This relationship may be due to the fact that infants are partially protected earlier in life by the antibodies from their mothers and passive transfer of the same antibodies through

breastfeeding (Dobbs and Dent, 2016; Teo et al., 2016). Hendriksen et al., (2013) (Hendriksen et al., 2013) reported similar findings.

Social economic status was negatively correlated with malaria risk. Children living in wealthier households had a significantly lower malaria risk compared to those living in poorer households. This finding is expected because wealthier people are more likely to afford better health services and afford adequate housing facilities with screens that block mosquitoes resulting in reduced transmission. This finding confirms previous results that showed that malaria burden is highly correlated with poverty (Owens, 2015).

Furthermore, higher mother's education was associated with reduced malaria prevalence. The role of education in disease prevention cannot be overstated. Highly educated mothers in addition to being more likely to have better socioeconomic means, are also most likely to have knowledge and means to afford malaria preventive measures. This finding is in agreement with results reported by Fana et al., (2015)(Fana et al., 2015). However, mother's education had no effect on malaria prevalence in Burkina Faso (Diboulo et al., 2016).

Results also showed that effects of intervention vary with region - which partially may explain wide variations in malaria prevalence among regions in spite of a high coverage of ITN. Despite the lack of country-level effect for ITN use, the effect of this intervention is significant in the Mid-western region. The varying effects of interventions in different regions may be explained by differences in regions with respect to ecological settings, access to health services, and socio-economic development which are important drivers of malaria transmission. Similar findings were reported in Burkina Faso (Diboulo et al., 2016), Angola, Liberia, Mozambique, Rwanda, Senegal, and Tanzania (Giardina et al., 2014).

The high malaria prevalence burden predicted for East Central region can be attributed to rice growing (Pullan et al., 2010) which is a predominant economic activity in this region. The rice paddies in which rice is grown serve as suitable habitats for malaria vector breeding.

Similarly, the high parasitaemia burden in the North East and West Nile may be due to a very low access to health services (Yeka, 2012) and high poverty levels in these regions (Ministry of Finance, 2014). On the other hand, a low malaria burden in Kampala region (capital city) can be attributed to better socio-economic conditions (Ministry of Finance, 2014), reduction in potential mosquito breeding sites as swamps are reclaimed for residential houses construction (Mukwaya et al., 2010), and a high access to health services (Kiwanuka et al., 2008). In South-western region, malaria is low largely due to its location in highlands whose lower temperatures negatively affect vector survival (Yeka, 2012).

The risk map illustrates the contemporary malaria situation in the country and can be used for planning, implementation, resource mobilization, monitoring and evaluation of interventions in the country. This map differs from that extracted from the 2010 world malaria MAP (Gething et al., 2011) although the outright comparison between these two maps is not possible majorly due to differences in malaria metrics estimated and data sources used. The map from the current study estimates malaria prevalence in the group of children less than 5 years only, whereas the world malaria MAP estimates the burden in the whole population. However, the malaria map produced in this study shows considerable shrinkage in malaria burden in comparison to results from the first MIS survey of 2009 that showed a high burden of malaria in the whole country with the exception of Kampala and highland areas in South Western region (Uganda Bureau of Statistics and ICF International, 2010).

There are some limitations of the current study that should be taken into account when interpreting these findings. Firstly, the current study relied on malaria test results from microscopy instead of the gold standard molecular method of polymerase chain reaction (PCR) which is more sensitive than microscopy. Secondly, prediction using spatial methods for data collected from population-weighted sampling designs as the case in MIS may produce imprecise

estimates as areas expected to have higher malaria risk are undersampled resulting in higher prediction errors (Jacquez, 2004).

Furthermore, we did not rescale the varying spatial resolutions of the environmental/climatic remote sensing proxies to a common scale prior to adding them to the models. This may lead to invalid inferences of our study estimates (Gotway and Young, 2002).

2.5 Conclusions

This study has demonstrated that IRS and ITN ownership are important interventions against malaria prevalence in children less than 5 years in Uganda, but the effects of all intervention vary by region. Varying intervention effects across regions indicate that interventions do not have a similar effect in different regions. This calls for epidemiological and entomological research in the different settings of the regions to determine the best tools suitable for each region. As well as scaling up of IRS intervention in areas of high transmission and replacing worn-out ITNs with new ones, the government should further strengthen the health system especially in rural areas, embark on socio-economic transformation programs, and introduce new tools such as environmental modification because of the role of these factors on malaria burden in the country.

Acknowledgments

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2.6 Appendix

Statistical modeling details

Let Y_{ij} be a binary outcome variable taking value 1 or 0 if a child *i* at location s*j* tested positive for malaria. Y_{ij} is assumed to follow a Bernoulli distribution $Y_{ij} \sim Ber(p_{ij})$ and is related to its predictors using a logistic regression model as follows; $\log it(p_{ij}) = \beta_0 + \sum_{k=1}^{K} \beta_k X_{ij}^{(k)} + \phi_j$ + wi where p_{ij} is the risk of child i at location s_j of having malaria, $\boldsymbol{\beta} = (\beta_0, \beta_1, ..., \beta_K)^T$ is the vector of K regression coefficients. Employing a geostatistical model formulated in (Cressie, 2015), spatial dependence is introduced by adding location-specific random effects f_j at every sampled location s_j modeled by a Gaussian process, $\boldsymbol{\varphi} = (\varphi_0, \varphi_1, ..., \varphi_K)^T \sim N(0, \Sigma)$ where $\sum$ is the variance-covariance matrix and each element is defined by an exponential parametric function of the distance d_{ij} between two location s_j and s_l, that is, $\sigma^2 \exp(-d_{ij} r)$. The parameter σ^2 is the spatial variation and r is a smoothing parameter that controls the rate of correlation decay with increasing distance. For exponential correlation function, the range parameter calculated as $3/r$ is an estimate of the minimum distance beyond which spatial correlation is negligible. Non-spatial variation is estimated by the random effects wi, assumed independent and normally distributed with mean 0 and variance σ^2_w. Model fit, parameter estimation and prediction was done using Bayesian formulation and MCMC estimation. Model specification was completed by assigning prior distributions to model parameters. - An inverse-gamma prior for the variance, a gamma distribution for the spatial decay parameter, and non-informative Gaussian distributions for regression coefficients with mean 0 and variance 100.

To identify the best set of predictor variables and their functional form Bayesian variable selection was done using Spike and Slab approach (Chammartin et al., 2013). For every predictor X_p a categorical indicator parameter I_p was introduced and indicating exclusion of the

predictor from the model ($I_p = 0$), inclusion in linear ($I_p = 1$) or categorical form ($I_p = 2$). I_p has a probability mass function $\prod_{j=0}^{2} \pi_j^{\delta_j(I_p)}$ where π_j are the inclusion probability of functional form j (i.e. $j = 0,1,2$) such that $\sum_{j=0}^{2} \pi_j = 1$ and $\delta_j(\cdot)$ is the Dirac function, $\delta_j(I_p) = \begin{cases} 1 & if \ \ I_p = j \\ 0 & if \ \ I_p \neq j \end{cases}$. In addition, a spike and slab prior was assumed for the corresponding regression coefficient. For the coefficient β_p of the predictor in linear form we take $\beta_p \sim \delta_1(I_p) N(0, \tau_p^2) + \left(1 - \delta_1(I_p)\right) N(0, \upsilon_0 \tau_p^2)$ proposing a non-informative prior for β_p in case $\underset{\sim}{X}_p$ is included in the model in linear form (slab) and an informative normal prior shrinking β_p to zero (spike) if $\underset{\sim}{X}_p$ is excluded from the model. Similarly, for the coefficient $\{\beta_{p,l}\}_{l=1,...L}$ corresponding to the categorical form of $\underset{\sim}{X}_p$ with L categories, we assume that $\beta_{p,l} \sim \delta_2(I_p) N(0, \tau_{p,l}^2) + \left(1 - \delta_2(I_p)\right) N(0, \upsilon_0 \tau_{p,l}^2)$. For the inclusion probabilities, we adopt a non-informative Dirichlet distribution with hyper-parameter $\alpha = (1,1,1)^T$ that is, $\pi = (\pi_0, \pi_1, \pi_2)^T \sim Dirichlet(3, \alpha)$. For better correlation properties and speed up MCMC computational time, continuous covariates were standardized.

Model parameters were estimated using MCMC simulation (Gibbs sampling). Starting with some initial values for the parameters, two chains sampler were run discarding the first 5000 iterations. Convergence was assessed by Gelman and Rubin diagnostic (Gelman and Rubin, 1992) and kernel density plots were used to assess for convergence of the chains.

Estimating the effect of intervention at regional level

The model above was extended to include intervention coverage effects with spatially varying coefficients, that is: $\log it(p_{ij}) = \beta_0 + \sum_{k=1}^{K} \beta_k X_{ij}^{(k)} + \sum_{m=1}^{M} b_{mj} Z_i^{(m)}(A_j) + \phi_j$, where $Z_i^{(m)}(A_j)$ is the

m intervention coverage aggregated over region A_j of the s_j location, b_{mj} is the corresponding spatially varying coefficient (i.e. intervention effect at A_j region) and M is the number of spatially varying interventions. Gaussian conditional autoregressive (CAR) prior distributions were assumed for the $\boldsymbol{b}_m$, that is $\boldsymbol{b}_m \sim N(b_{m0}\mathbf{1}, \boldsymbol{\Sigma}_m)$ where b_{m0} is the global effect of the m intervention at country level and $\boldsymbol{\Sigma}_m^{-1} = \sigma_m^{-2}(D - W)$, D is a diagonal matrix with elements, the sum of the neighbours of each region, W is a proximity matrix.

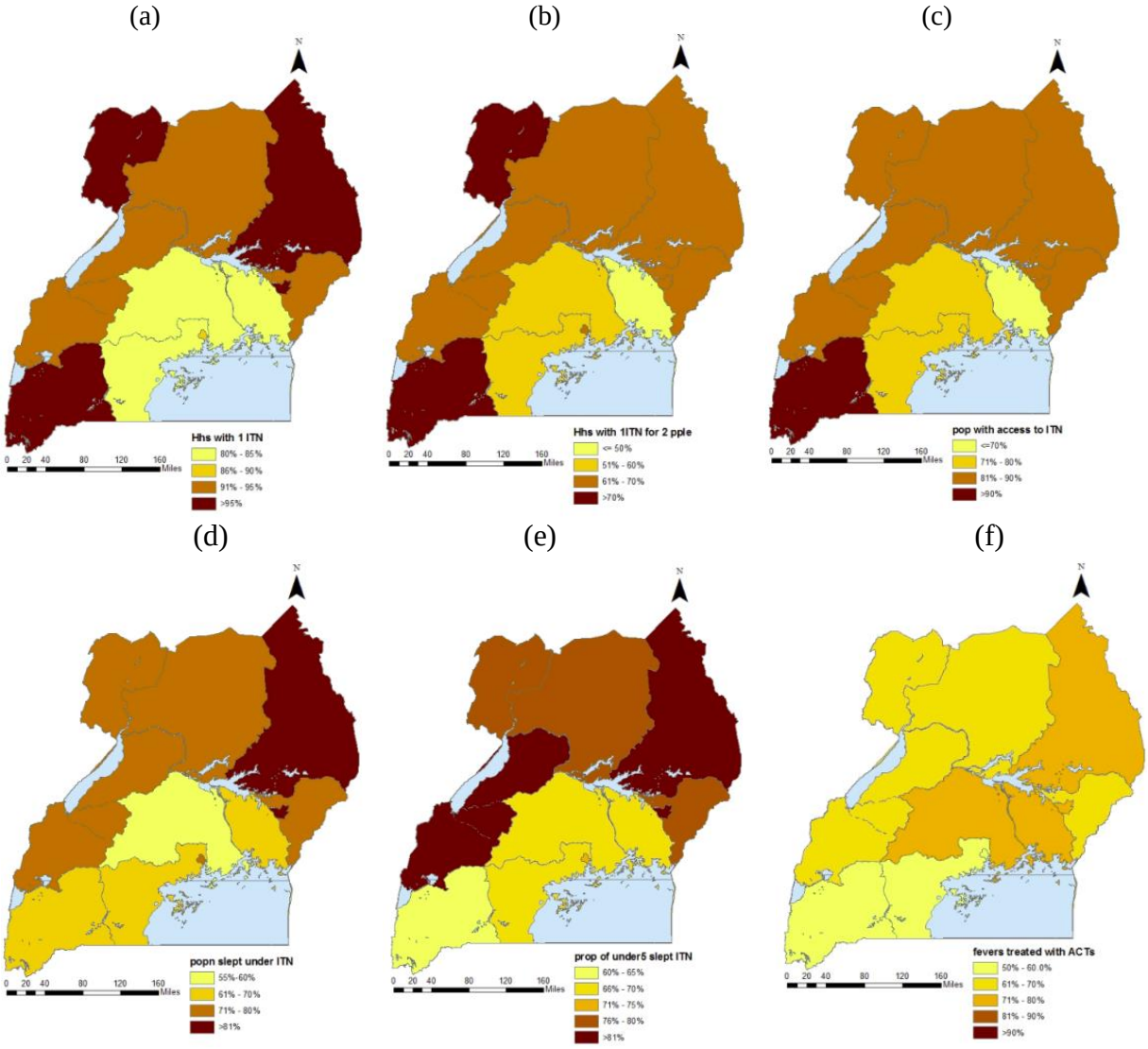

Figure 2.4: Malaria intervention coverage in Uganda in 2014; (a) Prop of HHs with 1 ITN, (b) Prop of HHs with 1 ITN for two people, (c) Pop with access to an ITN, (d) Prop who slept under an ITN, (e) Prop under 5 slept who under ITN, (f) Prop of fevers with ACTs

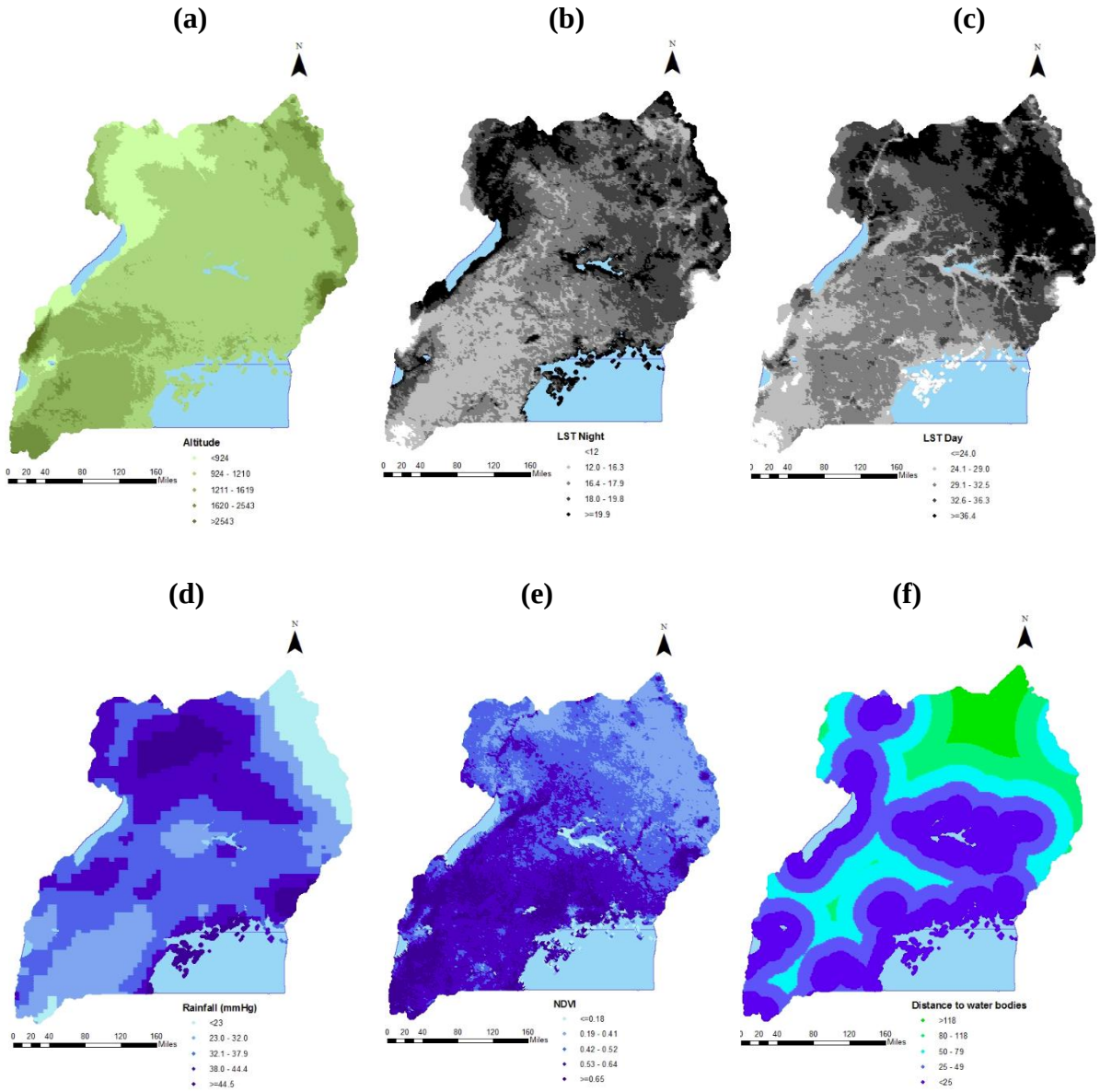

Figure 2.5: Distribution of climatic/environmental factors in Uganda in 2014; (a) Altitude, (b) Night LST, (c) Day LST, (d) Rainfall, (e) NDVI, (f) Distance to water bodies

Chapter 3: The contribution of malaria control interventions on spatio-temporal changes of parasitaemia risk in Uganda during 2009–2014

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Abstract

Background

In Uganda, malaria vector control interventions and case management with Artemisinin Combination Therapies (ACTs) have been scaled up over the last few years as a result of increased funding. Data on parasitaemia prevalence among children less than 5 years old and coverage of interventions was collected during the first two Malaria Indicator Surveys (MIS) conducted in 2009 and 2014, respectively. In this study, we quantify the effects of control interventions on parasitaemia risk changes between the two MIS in a spatio-temporal analysis.

Methods

Bayesian geostatistical and temporal models were fitted on the MIS data of 2009 and 2014. The models took into account geographical misalignment in the locations of the two surveys and adjusted for climatic changes and socio-economic differentials. Parasitaemia risk was predicted over a 2×2 km^2 grid and the number of infected children less than 5 years old was estimated. Geostatistical variable selection was applied to identify the most important ITN coverage indicators. A spatially varying coefficient model was used to estimate intervention effects at a sub-national level.

Results

The coverage of Insecticide Treated Nets (ITNs) and ACTs more than doubled at country and sub-national levels during the period 2009–2014. The coverage of Indoor Residual Spraying (IRS) remained static at all levels. ITNs, IRS, and ACTs were associated with a reduction in parasitaemia odds of 19% (95% BCI: 18–29%), 78% (95% BCI: 67–84%), and 34% (95% BCI: 28–66%), respectively. Intervention effects varied with region. Higher socioeconomic status and living in urban areas were associated with parasitaemia odds reduction of 46% (95% BCI: 0.51–0.57) and 57% (95% BCI: 0.40–0.53), respectively. The probability of parasitaemia risk decline in the country was 85% and varied from 70% in the North-East region to 100% in Kampala

region. The estimated number of children infected with malaria declined from 2,480,373 in 2009 to 825,636 in 2014.

Conclusions

Interventions have had a strong effect on the decline of parasitaemia risk in Uganda during 2009–2014, albeit with varying magnitude in the regions. This success should be sustained by optimizing ITN coverage to achieve universal coverage.

Keywords: Malaria, Malaria indicator survey, Spatio-temporal, Parasitaemia, ITNs, IRS, ACTs, Spatially varying, Bayesian kriging, Malaria interventions

3.1 Introduction

Although malaria is still a leading global health problem, its burden has been on a decline in recent years (World Health Organization, 2016). This decline which started in the early 1990s prior to the global campaign of scaling up of control interventions in mid-2000s continued through the post-scale-up period (Snow et al., 2015). The downward trend of malaria burden in the pre-intervention period notwithstanding, sufficient evidence from randomized trials and field settings indicate that malaria decline during the post-scale-up period has been unprecedented (Bhatt et al., 2015a; Bhattarai et al., 2007; Lengeler, 2004; Snow et al., 2015). For instance in sub-Saharan Africa (SSA), parasitaemia prevalence declined from 17% in 2010 to 13% in 2015 (World Health Organization, 2016). Also, during the period 2000-2015, declines in global malaria incidence and deaths of up to 37% and 60%, respectively were reported (Bhatt et al., 2015a; WHO and UNICEF, 2015). These declines were mainly attributed to the impact of Insecticide Treated Nets (ITNs) and malaria case management with Artemisinin Combination Therapies (ACTs).

In spite of these higher declines in malaria at the global level, slower declines were reported in the 15 most high burden countries, the majority of which are situated in SSA(World Health Organization, 2015a). This region bears the heaviest burden and accounts for an estimated 90% of all malaria deaths mainly among children less than 5 years. Uganda is ranked fourth among these high malaria burden countries and has some of the highest malaria transmission rates in the world (President's Malaria Initiative, 2017).

Since 2006, Roll Back Malaria (RBM) has funded malaria control and prevention activities in the country and periodically supports the conducting of Malaria Indicator Surveys (MIS) (National Malaria Control Program, 2016). The MIS are standardized nationally representative surveys that collect high-quality data for estimating the prevalence of parasitaemia risk in children less than 5 years and track the progress of interventions coverage. To date, two

MIS have been conducted in Uganda; MIS 2009 and MIS 2014-15 (Uganda Bureau of Statistics and ICF International, 2015, 2010). Findings from the first MIS revealed a high parasitaemia risk in most regions. Malaria was hyperendemic (prevalence 50%-75%) in three regions, mesoendemic (prevalence 10%-50%) in six, and only hypoendemic (prevalence <10%) in one region (Uganda Bureau of Statistics and ICF International, 2010). Results of the second MIS showed tremendous improvement in the coverage of ITNs and ACTs intervention at all levels and a reduction of parasitaemia risk of 50%. Additionally, parasitaemia risk in the majority of regions had declined to mesoendemic and hypoendemic proportions (Uganda Bureau of Statistics and ICF International, 2015). The true effect of each intervention on parasitaemia reduction is not known at national and sub-national level, and yet a new framework has been adopted by the Ministry of Health (MoH) to speed up malaria control efforts. In this framework known as Uganda Malaria Reduction Strategic Plan (UMRSP) 2014-2020, ambitious targets have been set to reduce malaria mortality to near zero, morbidity to 30 cases per 1,000 population, and parasite prevalence to less than 7% (National Malaria Control Program, 2016). To achieve these targets and ensure efficient use of scarce resources and effective programming and implementation, it is vital to understand the effect that each intervention has had on parasitaemia risk decline.

Declines in malaria parasitaemia risk, morbidity and mortality have been achieved in other malaria-endemic countries following scaling up of control interventions. Bhat et al., 2015 (Bhatt et al., 2015a) reported a reduction of 50% in *Plasmodium falciparum* prevalence and 40% in the incidence of clinical disease in endemic African countries between 2000 and 2015. Similarly, the number of malaria cases and deaths decreased by more than 50% in southern African countries after introducing interventions during 2000-2008 (O'Meara et al., 2010). In the Kilifi district of Kenya, parasitaemia prevalence declined from 35% to 1% after a mass distribution of ITNs and ACTs (O'Meara et al., 2010). Also, Giardina et al., (2014) (Giardina et

al., 2014) demonstrated that ITNs and IRS were significantly associated with parasitaemia risk reduction in Rwanda, Tanzania, Senegal, Angola, Liberia and Mozambique.

Our study aims to estimate spatio-temporal trends of parasitaemia risk changes among children less than 5 years in Uganda during 2009–2014, and to determine the effect of interventions on parasitaemia risk decline at national and subnational levels. We analyzed MIS data using Bayesian spatio-temporal geostatistical models. The results from this study provide insight on the effectiveness of interventions and can be used by MoH and Malaria Control Program (MCP) to evaluate interventions and optimize resources for the achievement of objectives of UMRSP 2014-2020.

3.2 Methods

3.2.1 Country profile

Uganda is located in the great lakes region in East Africa neighboring Kenya, Tanzania, Rwanda, Democratic Republic of Congo, and South Sudan. It has a population of 37.1 million, all of which are at risk of malaria. Malaria is the leading cause of morbidity and mortality in the country, accounting for 3,631,939 (4,400,000 – 12,000,000) cases and 5,921 (5,300 – 17,000) deaths in 2015 (WHO, 2015). The most dominant malaria parasite is *Plasmodium falciparum*, and the major transmission vectors are *Anopheles gambiae* and *Anopheles funestus*. In recent times, vector resistance to both pyrethroid and carbamates has been reported.

3.2.2 Data sources

Parasitological and interventions data were obtained from the MIS data of 2009 and 2014-15. The two surveys were conducted at the peak of a high malaria transmission season towards the end of the long rainy season (December 2009 and December 2014-January 2015, respectively). The MIS are nationally representative surveys which employ a two-stage stratified cluster design. The clusters also known as census enumeration areas are selected at first stage with probability-proportional-to-size sampling, and households are selected at second stage using systematic sampling. The surveys are designed to provide information on key malaria control

indicators, such as the proportion of households having at least one ITN, the proportion of children under 5 who slept under an ITN the previous night. Also, the survey is designed to produce representative key indicator estimates key for urban and rural strata separately, as well as for the ten regions that constitute the country. The regions are; Kampala, Central 1, Central 2, East Central, Mid North, Mid-Western, Mid-western, North East, South Western and West Nile. At the first stage of sampling, 170 and 210 clusters were selected in 2009 and 2014, respectively. At the second stage, 28 households were selected from each cluster in both surveys resulting in a total of 4,000 and 5,880 households selected in the first and second survey, respectively (Uganda Bureau of Statistics and ICF International, 2015, 2010).

Coverage of ITNs was defined in terms of ownership and use indicators that were generated from data captured on the survey tools using standard definitions (World Health Organisation, 2013). The following ITN ownership indicators were defined; the proportion of households with at least one ITN, the proportion of households with one ITN for every two people, and the proportion of population with access to an ITN within their household. The ITN use indicators were; the proportion of children less than 5 years who slept under an ITN, the proportion of population that slept under an ITN, and the proportion of ITNs used the night preceding the survey. IRS coverage was defined as the proportion of households that were sprayed during the last 12 and 6 months in the MIS 2009 and MIS 2014-15, respectively. The wealth index derived from household possessions was used as a socioeconomic proxy. A case management indicator was defined as the proportion of fever episodes in children of less than 5 years during the last two weeks preceding the survey which were treated with any Artemisinin Combination Therapies (ACTs). In addition, information on the location of the cluster (i.e. rural/urban) was obtained from survey data and from the Global Rural-Urban Mapping Project (GRUMP) database ("Global Rural-Urban Mapping Project (GRUMP), v1 | SEDAC," 2017) . The GRUMP database provides gridded data at $1km^2$ spatial resolution.

Malaria transmission depends on the environment which affects the disease distribution, seasonality, and transmission intensity. Environmental/ climatic factors were extracted from Remote Sensing (RS) sources. Weekly day and night Land Surface Temperature (LST), bi-weekly Normalized Difference Vegetation Index (NDVI) and land cover data were obtained from Moderate Resolution Imaging Spectroradiometer (MODIS) at 1 km^2 spatial resolution. Dekadal rainfall data at 8x8 km^2 resolution were extracted from the US Early Warning and Environmental Monitoring System (EWES). Altitude was obtained from the shuttle radar topographic mission using the digital elevation model. Also, distances from cluster centroid to major water bodies were estimated using ESRI's ArcGIS 10.2.1 for Desktop. The high spatial resolution population data was downloaded from WorldPop (Worldpop dataset download, 2016).

Data from remote sensing sources was acquired for the 12 month period preceding the survey and the average (cumulative value for rainfall) was calculated and extracted for each cluster. The one-year period was considered long enough to capture the actual climatic conditions that affected malaria transmission throughout the year of the survey.

3.2.3 Statistical analysis

Bayesian geostatistical models were developed to predict parasitaemia risk at the two survey time points using environmental/climatic factors as predictors. Bayesian kriging was applied to obtain parasitaemia risk estimates over a 2x2 km^2 resolution grid. Predictions were used to determine the probability of parasitaemia risk reduction between the two surveys.

The number of children infected with malaria in the two surveys was estimated by combining high spatial resolution population data obtained from WorldPop (www.worldpop.org) with the predicted pixel-level malaria prevalence estimates. The number of children less than 5 years was estimated by multiplying population counts by a factor of 17.7%, the proportion of the population under 5 years (Uganda Bureau of Statistics, 2016). Regional estimates of the number of infected children were computed by aggregating pixel-level estimates at the regional level. The number of infected children per pixel was obtained by multiplying pixel-wise spatially

explicit prevalence estimates with high spatial resolution population estimates of the number of children less than 5 years. In both surveys, the population-adjusted prevalence was estimated by summing up estimates of the number of infected children per pixel divided by the total estimated number of children less than 5 years.

The effects of interventions were estimated by modeling the change of parasitaemia risk between the two surveys on the logit scale as a function of the effect of intervention coverage at the second survey adjusted for socioeconomic status, cluster location, and the difference in environmental/climatic factors. Geographical misalignment of the locations between the two surveys was carried out by predicting parasitaemia risk of the first survey at the second survey locations. The prediction uncertainty was incorporated by fitting an error term in the model. A spatially varying coefficients model was used to estimate intervention effects at regional level and to account for potential interactions of interventions with endemicity level.

A spike and slab geostatistical Bayesian variable selection procedure was applied to select the most important ITN and environmental predictors that explain maximum variation in the change in parasitaemia risk between 2009 and 2014 (Chammartin et al., 2013). Variables with the highest inclusion probability in the model were selected.

Descriptive analyses were carried out in STATA (StataCorp. 2015. *Stata Statistical Software: Release 14*. College Station, TX: StataCorp LP). Geostatistical modeling was implemented in OpenBUGS version 3.2.3 (Lunn et al., 2000). Since implementing Bayesian kriging in OpenBUGS is very slow especially for large grids, we implemented it in R statistical software using posterior estimates of the model parameters obtained from OpenBUGS. Maps were produced in ESRI's ArcGIS 10.2.1 (http://www.esri.com/).

Parameter estimates were summarized by their posterior medians and their corresponding 95% Bayesian Credible Intervals (BCI). The effect of a predictor was considered to be statistically important if its 95%BCI did not include zero.

Detailed explanations of the fitted statistical models are presented in the Appendix.

3.3 Results

3.3.1 Descriptive results

A summary of the survey data is given in Tables 1 and 2, and maps of survey locations are presented in Figures 3.1 and 3.2. A higher number of clusters, households, and children were tested in the second survey (Table 3.1).

Table 3.1 Survey information and malaria intervention coverage indicators in 2009 and 2014

Indicator	MIS 2009	MIS 2014–2015
Number of clusters	170	210
Number of households	4,421	5,345
Number of children tested	3,972	4,939
Interventions	**% (95%CI)**	**% (95%CI)**
Parasitaemia prevalence	42.4 (37.7–47.0)	19.0 (16.3–21.8)
Proportion of households with at least one ITN	46.7 (42.7–50.6)	90.2 (88.7–91.7)
Proportion of households with at least one ITN for every two people	16.4 (14.2–18.5)	62.3 (60.1–64.5)
Proportion of population with access to an ITN in their household	32.2 (29.3–35.1)	80.6 (78.9–82.4)
Proportion of the population that slept under an ITN the previous night	26.3 (23.5–29.2)	70.8 (68.9–72.8)
Proportion of children less than 5 years old who slept under an ITN the previous night	32.9 (29.0–36.9)	74.5 (72.2–76.9)
Proportion of existing ITNs used the previous night	26.1 (23.3–28.9)	70.4 (68.5–72.4)
Proportion of households sprayed in the last 6 months	5.5 (3.0–7.9)	5.2 (3.4–6.9)
Proportion of households with at least one ITN and/or sprayed by IRS in the last 12 months	49.2 (45.3–53.1)	90.5 (89.0–92.0)
Proportion of fever episodes treated with ACT	23.3 (19.9–26.7)	66.8 (63.2–70.5)

Abbreviations: MIS, Malaria Indicator Survey; TNs, Insecticide Treated Nets; ACTs, Artemisinin Combination Therapies; IRS, Indoor Residual Spraying

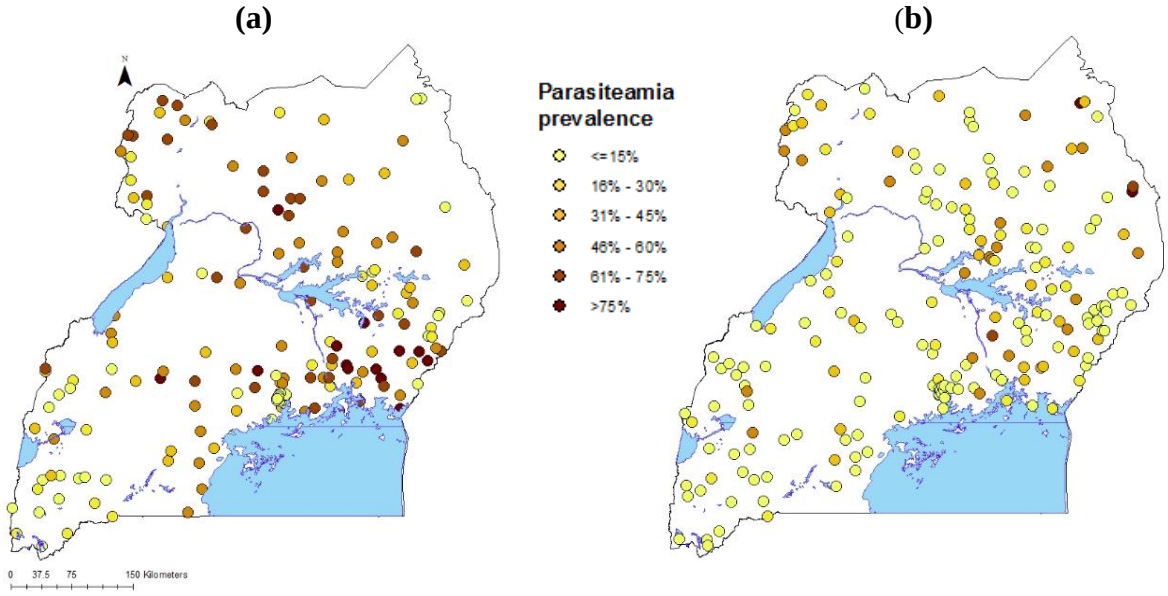


Figure 3.1: Observed malaria prevalence and survey locations of MIS 2009 (a) and MIS 2014–15 (b)

Table 3.2: Coverage of malaria intervention coverage indicators by region in 2009 and 2014

Indicator	Central 1		Central 2		Kampala		East-Central		Mid-Eastern		North-East		Mid-North		West Nile		Mid-Western		South-Western	
	2009	2014	2009	2014	2009	2014	2009	2014	2009	2014	2009	2014	2009	2014	2009	2014	2009	2014	2009	2014
Parasitaemia prevalence	39.0	10.4	51.0	23.6	4.9	0.4	56.2	36.4	37.4	13.5	39.7	27.2	62.1	19.5	45.6	27.5	42.7	17.5	11.8	4.1
Proportion of households with at least one ITN	35.3	80.8	23.5	81.6	49.1	86.3	33.5	82.1	59.5	94.6	76.6	97.0	63.7	94.3	52.4	96.3	33.9	93.6	33.7	96.9
Proportion of households with at least one ITN for every two people	14.6	56.7	9.3	53.4	32.4	66.5	7.8	46.7	17.0	61.7	33.1	60.6	20.1	66.7	12.8	72.1	12.1	64.0	14.7	76.6
Proportion of population with access to an ITN	25.4	71.8	16.4	70.8	42.4	79.2	21.6	68.7	37.1	83.7	57.0	84.2	43.7	85.8	33.0	88.8	23.0	83.7	30.0	91.1
Proportion of the population that slept under an ITN	19.1	60.1	10.3	58.6	36.9	73.0	18.7	62.8	31.4	76.3	54.3	85.5	32.1	77.6	33.1	77.7	17.0	78.6	22.6	67.0
Proportion of children less than 5 years old who slept under an ITN	21.5	67.6	11.3	65.3	42.5	73.9	19.3	69.7	41.4	78.8	65.1	87.0	41.7	79.0	37.2	76.8	20.4	82.3	33.1	64.4
Proportion of existing ITNs used the previous night	19.1	59.6	10.3	58.5	36.7	72.7	18.7	62.6	31.1	75.9	52.5	84.3	32.0	77.1	32.9	77.0	16.8	78.5	22.6	66.6
Proportion of households sprayed	0.2	1.0	4.6	0.4	5.5	1.3	0.4	0.0	0.6	0.4	4.2	0.1	31.6	44.6	0.0	1.2	0.2	0.3	1.8	0.0
Proportion of households with at least one ITN and/or sprayed by IRS in the last 12 months	35.3	80.8	26.3	81.9	52.3	86.3	33.8	82.1	59.6	94.6	77.1	97.0	77.8	97.2	52.4	96.3	34.1	93.6	44.7	96.9
Proportion of fever episodes treated with any artemisin combination therapy	17.4	55.2	18.0	71.7	22.5	51.5	13.4	71.1	16.6	68.0	25.1	73.3	40.8	69.2	27.7	67.0	19.4	61.1	10.0	53.3

Results show that at country level parasitaemia prevalence declined from 42.4% in 2009 to 19.0% in 2014, a decline of 50%. At the regional level, the highest malaria reduction was observed in the regions of Kampala (91.8%), Central 1 (74.0%) and Mid-North (68.6%), and the lowest in North East (30.2%) and East Central region (35.2%).

Generally, interventions coverage increased at country and regional levels (Appendix). At the country level, ITN ownership (the proportion of households with at least one ITN and the proportion of households with at least one ITN for every two people) increased by four-fold. Among regions, the biggest increase in ITN ownership was reported in East Central (six-fold), while the smallest was observed in Mid-North (two-fold). More so, the proportion of children less than 5 years that slept under an ITN increased by more than two times at country level. The improvement in this indicator coverage was highest in Central 2 region (5.8 times) and lowest in North East (1.3 times).

Overall, the proportion of fever episodes treated with ACTs increased by three times. The highest increase was achieved in South Western, East Central and West Nile regions where coverage increased by more than five times. The least gain in ACTs coverage was observed in Mid North region where it increased by almost two times. The national IRS coverage remained static at 5% except in the Mid North region where an increase of 41% was achieved.

3.3.2 Spatio-temporal trends of parasitaemia risk during 2009 - 2014

The effects of the most important environmental factors identified through geostatistical variable selection are shown in Table 3.3. Results indicate that more environmental factors were related to parasitaemia risk in 2009 compared to 2014. Also, the spatial correlation was stronger in 2009.

Figure 3.2 depicts the predicted parasitaemia risk for 2009 and 2014 based on environmental/climatic factors over a 2x2 km^2 resolution grid. Estimates suggest a high parasitaemia risk in 2009 where in some areas the predicted prevalence was over 80%.

In 2014, parasitaemia risk was much lower in most parts of the country except in some areas of the East Central, North East, and West Nile regions where the burden still remained high.

Table 3.3: Posterior estimates of the effect of environmental factors on parasitaemia risk in 2009 and 2014

Predictor	MIS 2009	MIS 2014-15
	OR (95%BCI)	OR (95%BCI)
Day LST[a]		
< 27.84 / < 31.4	1	1
27.84–30.18 / 31.4–33.8	1.68 (1.44–2.14)*	2.75 (2.03–3.64)*
> = 30.19 / > = 33.8	1.41 (1.28–1.76)*	2.19 (1.79–3.39)*
Night LST	1.55 (1.39–1.67)*	1.44 (1.19–1.60)*
Area type		
Rural vs urban	7.80 (4.88–11.09)*	3.70 (2.56–4.88)*
NDVI	1.25 (1.10–1.51)*	
Rainfall[a]		
< 17.11 / < 17.14	1	
17.11–18.49 / 17.14–18.79	1.13 (0.93–1.23)	
> = 18.50 / > = 18.79	1.39 (1.12–1.49)*	
Altitude[a]		
< 1098	1	
1098–1201	0.89 (0.81–0.95)*	
> = 1202	0.43 (0.38–0.47)*	
Land cover		
Others		1
Crops		1.19 (1.13–1.43)*
Spatial parameters		
Spatial variance	1.12 (0.99–1.20)	0.54 (0.49–0.59)
Range (km)	43.3 (12.2–57.8)	43.8 (36.3–48.2)

*****Statistically important effect

[a]Cut-offs before and after the slash (/) are for 2009 and 2014 respectively

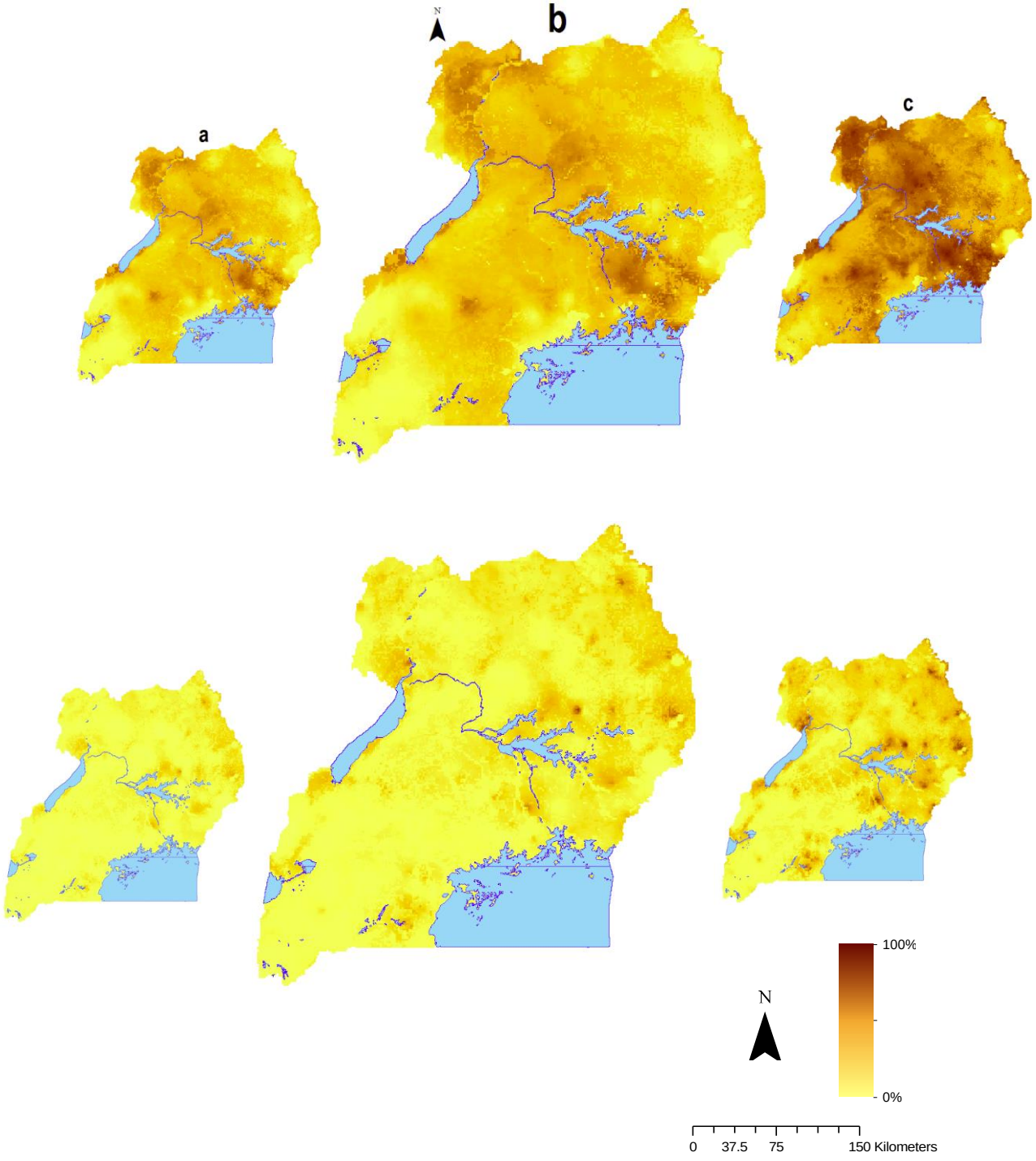


Figure 3.2: Predicted parasitaemia risk in 2009 and 2014. 2.5th percentile posterior predictive distribution (a), median posterior predictive distribution (b), 97.5th percentile posterior predictive distribution (c)

The probability of parasitaemia decline in the country was 85%. The highest decline in malaria occurred in the regions of Central 2 and Kampala while the least was estimated in the North East region (Figure 3.3).

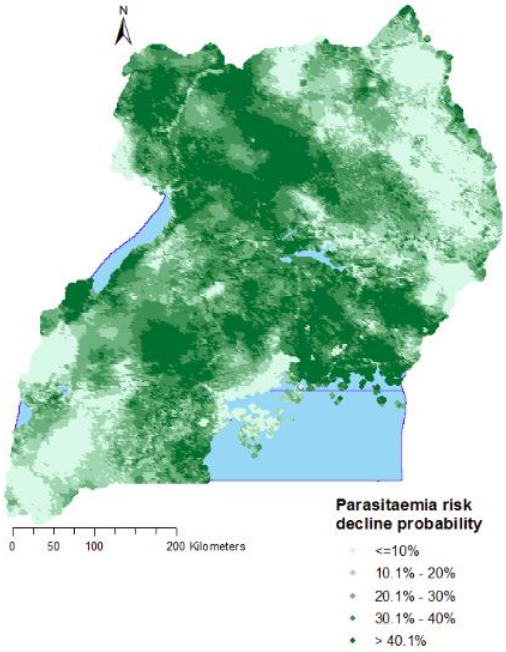


Figure 3.3: Probability of parasitaemia risk decline from 2009 to 2014

Overall, the number of infected children reduced from over 2,480,000 to less than 830,000 between 2009 and 2014 (Table 3.4). This translates into a reduction of over 66%. Reduction in the estimated number of infected children was achieved in all regions.

Table 3.4: Estimated number of infected children and population adjusted prevalence in 2009 and 2014

Region	No. of infected children in 2009	No. of infected children in 2014	Percentage reduction in no. of infected children	Population adjusted prevalence in 2009	Population adjusted prevalence in 2014	Population adjusted prevalence difference
			(%)	% (95% BCI)	% (95% BCI)	(%)
North-East	212,159	119,871	43.5	37.6 (37.4–37.8)	23.3 (23.1–23.4)	14.3
West Nile	276,237	106,377	61.5	56.8 (56.4–57.2)	25.8 (25.5–26.0)	31.0
Mid-North	332,162	98,846	70.2	52.4 (52.2–52.5)	20.0 (19.8–20.2)	32.4
Mid-Western	269,487	77,027	71.4	39.6 (39.3–39.9)	12.9 (12.7–13.1)	26.7
Mid-Eastern	274,376	79,734	70.9	46.3 (45.6–47.1)	16.8 (16.4–17.2)	29.5
East-Central	375,575	138,191	63.2	64.7 (64.3–65.1)	25.3 (24.8–25.8)	39.4
Central 2	338,097	87,562	74.1	50.1 (49.8–50.3)	14.4 (14.2–14.6)	35.7
Central 1	232,426	58,314	74.9	38.2 (37.8–38.6)	10.6 (10.4–10.8)	27.6
South-Western	148,799	56,819	61.7	22.2 (22.0–22.5)	8.8 (8.6–9.1)	13.4
Kampala	21,060	2,895	86.3	5.9 (5.2–6.5)	0.9 (0.8–1.1)	5.0
Overall	2,480,373	825,636	66.7	44.0 (43.9–44.2)	17.7 (17.6–17.7)	26.3

The biggest reduction occurred in Kampala (86%), Central 1 (75%), Central 2 (74%), Mid-Eastern (71%) and Mid North region (70%), whereas the least happened in North East (44%). In both surveys, the highest and lowest numbers of infected children were estimated in the East Central and Kampala regions, respectively.

Overall, a reduction in population adjusted-prevalence of over 26% was achieved. The highest reduction (39.4%) was observed in East Central while the least one (5.0%) was registered in Kampala.

Figure 3.4 further shows that the number of infected children in 2014 shrank considerably compared to 2009 in all regions except in the East Central region. The map also depicts a strong statistically important reduction in the concentration of infected children in Mid North region in 2014.

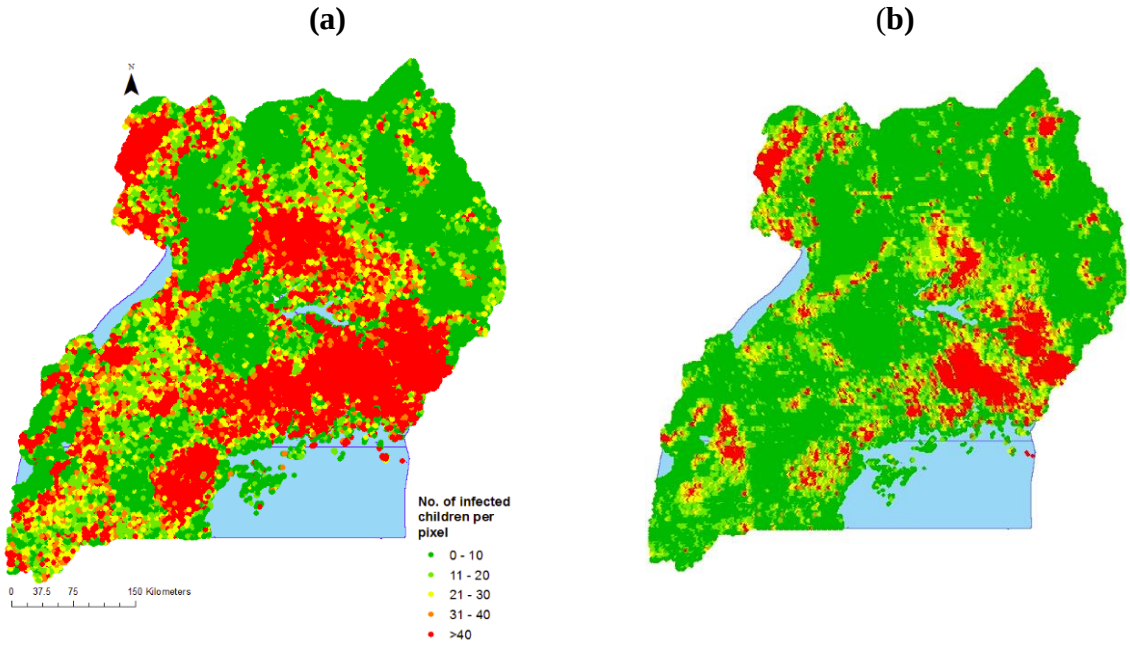


Figure 3.4: Distribution of estimated number of infected children per pixel in 2009 (a) and 2014 (b)

Results from geostatistical variable selection (Table 3.5) indicate that the proportion of the population with access to an ITN in their household was the only indicator able to capture the effect of ITN interventions as it has the highest inclusion probability. This indicator was used to quantify the effect of ITNs on the parasitaemia odds change.

Table 3.5: Posterior inclusion probability for ITN coverage indicator for MIS 2014

Indicator	Probability of inclusion (%)
Proportion of households with at least one ITN	5.8
Proportion of households with at least one ITN for every two people	6.1
Proportion of population with access to an ITN in their household	42.7
Proportion of the population that slept under an ITN the previous night	4.7
Proportion of children under five years old who slept under an ITN the previous night	12.3
Proportion of existing ITNs used the previous night	0.2

Abbreviations: MIS, Malaria Indicator Survey; ITN, Insecticide Treated Net

3.3.3 Effects of interventions on parasitaemia odds decline

The effects of interventions on the change of parasitaemia odds adjusted for socioeconomic status and changes in environmental conditions between the two surveys are shown in Table

3.6. Results demonstrate an important protective effect of interventions on the decrease of parasitaemia odds from 2009 to 2014. ITNs, IRS and ACTs were associated with a parasitaemia odds reduction of 19% (95%BCI: 18%-29%), 78% (95% BCI: 67%-84%), and 34% (95%BCI: 28%-66%), respectively.

Similarly, higher socio-economic status had a strong effect on parasitaemia odds reduction. More so, living in urban areas was associated with a decrease in malaria odds of 57% (95%BCI: 47-60%) compared to living in rural areas.

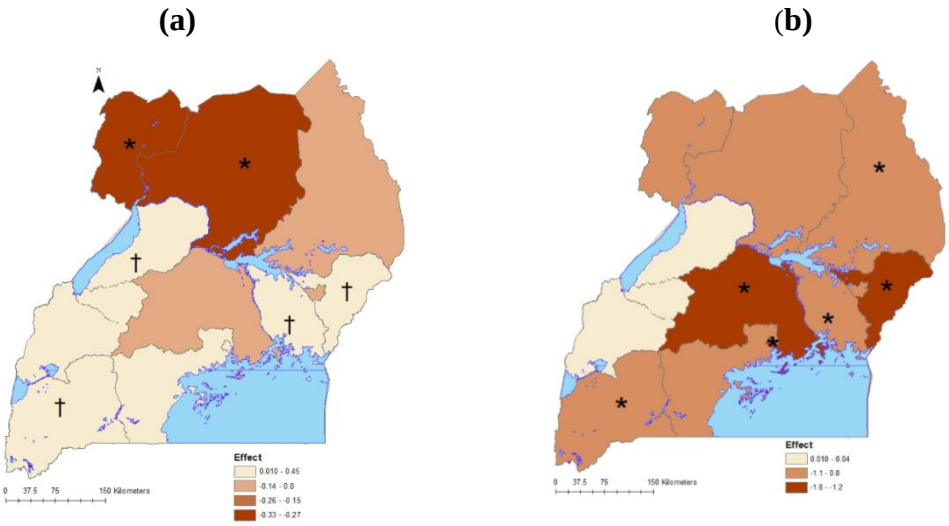
On average, rainfall, day and night LST increased from 2009 to 2014, and these increases were significantly associated with increased parasitaemia odds. However, changes in the NDVI had no effect on changes in parasitaemia odds.

Table 3.6: Posterior estimates for the effect of interventions adjusted for socio-economic status and changes in climatic/environmental conditions

Covariate	OR (95% BCI)
Difference in LST (day)	1.10 (1.02–1.13)*
Difference in LST (night)	1.09 (1.03–1.18)*
Difference in NDVI	1.00 (0.94–1.08)
Difference in rainfall	1.14 (1.08–1.23)*
Area type (urban vs rural)	0.43 (0.40–0.53)*
Wealth index	0.54 (0.51–0.57)*
ITN	0.81 (0.71–0.82)*
IRS	0.22 (0.16–0.33)*
ACTs	0.66 (0.34–0.72)*
Spatial variance	0.63 (0.56–0.76)
Range (km)	35.4 (24.3–37.0)

*Statistically important effect

Intervention effects on parasitaemia odds decline varied by region (Figure 3.5). The effect of ITNs at regional level was significantly higher than the national effect in Mid-North and West Nile. ITNs' effects were significantly lower in East Central, Mid-Eastern, Mid-Western, and South western. Likewise, the effect of ACTs was significantly higher than the national average in most regions except in Central 1, Mid North, Mid-Western, and West Nile.



** Statistically important effect higher than national effect*
† Statistically important effect less than national effect

Figure 3. 5: Spatially varying effects of interventions for ITNs (a) and ACTs (b)

3.4 Discussion

In this study, we have determined the spatio-temporal trends of parasitaemia odds and the effect of control interventions on the change of parasitaemia risk in Uganda during 2009-2014. Furthermore, we estimated the probability of parasitaemia risk decline and the number of infected children at the two survey time points.

Our study results showed a strong ITNs effect on parasitaemia risk reduction during 2009-2014 following a two-fold increase in coverage in the five years. These results support findings in similar malaria-endemic settings (Bhatt et al., 2015a). This protective effect can be attributed to the physical barrier provided by ITNs to block mosquitoes from infecting humans with *Plasmodium* sporozoites, thus preventing parasites from completing their development cycle (Bueno-Mari and Jimenez-Peydro, 2010). Also, the insecticide in ITNs reduce the lifespan of vectors when they come into contact, thus decreasing the chances of transmission (WHO and UNICEF, 2015). Furthermore, the high coverage and utilization registered in the country may have achieved a 'mass effect' that reduces the mosquito population and thus protects people in communities who are not using ITNs but live in close proximity to households with ITNs (Louis et al., 2012; Maxwell et al., 2002).

The high increase in ITNs coverage can be credited to increased donor support that funded ITNs purchase and distribution through effective distribution outreach channels (National Malaria Control Program, 2016). These channels include mass distribution campaigns, antenatal care clinics, Expanded Program for Immunization (EPI), and commercial sale of subsidized ITNs through the private sector. These distribution channels have had an immediate success of raising the proportion of households possessing at least one ITN from less than 50% to more than 90%. In spite of the high ITN coverage across the country, ITN effects on parasitaemia odds reduction varied with region. Effects were highest in regions which were initially the highest burdened in 2009. The varying effects of

interventions could be explained by regional heterogeneities in malaria transmission rates (Okello et al., 2006b), ecology, and access to health services (Yeka, 2012).

Furthermore, case management with ACTs was strongly associated with parasitaemia risk reduction following a three-fold increase in coverage during the study period. Prompt treatment of malaria with ACTs suppresses and kills malaria parasites in the body which prevents progression to severe disease, thus reducing transmission and subsequently parasitaemia load in the population (Baird, 2008). In line with our study findings, Bhat et al., 2015 (Bhatt et al., 2015a) also found that ACTs together with ITNs were the most impactful interventions on malaria risk reduction in African endemic countries during 2000-2015. Also, effects of ACTs also varied with region. However, despite the two-fold increase in ACTs coverage in the five years, its coverage was still lower than targeted. This could possibly be attributed to supply chain constraints (Kiwanuka et al., 2008), the semi-regulated private health facilities and drug stores and the inadequate laboratory diagnostic capacity in most of the lower level facilities (National Malaria Control Program, 2016).

Indoor residual house spraying also had a very strong effect on parasitaemia odds reduction despite its coverage remaining static between 2009 and 2014. The endophilic behavior of the predominant anopheles mosquito makes this intervention highly effective in Uganda as vectors are killed by the insecticide as they rest on house walls after taking a blood meal (Becker et al., 2010). The static coverage is perhaps explained by the high costs involved in IRS implementation. This prompted NMCP to roll out IRS gradually initially starting in 2009 with the 10 most high malaria burden districts located in the Mid-North region (National Malaria Control Program, 2016). Following a significant reduction in malaria transmission in the 10 districts (Bukirwa et al., 2009), IRS was later extended to another 14 high burden districts in the North East, Mid-Eastern, and East Central regions. The effectiveness of IRS on malaria risk reduction has been reported in other studies in Uganda (Bukirwa et al., 2009),

Kenya (Zhou et al., 2010), Bioko, Equatorial Guinea, and Mozambique (Kleinschmidt et al., 2009).

Our results further showed that urban areas were associated with a decreased parasitaemia risk compared to rural areas. This could be explained by uneven access to healthcare services between urban and rural areas in developing countries (Dolea, 2010). In Uganda, lower level health facilities which are the major source of health services in rural areas are poorly equipped and understaffed (Pariyo et al., 2009). On the other hand, urban areas are served by a much bigger network of better equipped higher level facilities both public and private. Indeed urbanization is one of the reasons that has been suggested as a strong possible causal factor of the downward trend of malaria risk in the pre-intervention period (Tatem et al., 2013). This has been attributed to the effect of urbanization on socio-economic and landscape changes which mitigates the risk of malaria transmission. The inverse relationship between urbanization and malaria risk has also been reported in other malaria-endemic settings (Omumbo et al., 2005; Ramroth et al., 2009; Tatem et al., 2013; Wang et al., 2005).

Higher socioeconomic status was strongly associated with parasitaemia odds reduction. Related to this finding, our results also showed that the highest probability of parasitaemia decline was attained in Kampala region and the lowest in the North East. The former is the capital city and the most developed region, while the latter is the least developed and most hard-to-reach region in Uganda. Socio-economic status affects the ability to afford healthcare services, better housing conditions, and knowledge of malaria prevention (Yadav et al., 2014) - which are important determinants of severity and outcome of the disease. These results are in agreement with other studies that reported a higher burden of malaria among poor countries (Snow and Marsh, 2010) [135]and in hard-to-reach areas (WHO and UNICEF, 2015). This finding augments evidence that malaria is a disease associated with poverty (Sachs, 2002; Tanner and de Savigny, 2008) and low socio-economic development (Feachem

and Sabot, 2008; Greenwood et al., 2008; Protopopoff et al., 2009; Tanner and de Savigny, 2008).

Furthermore, increased land surface temperature and rainfall between 2009 and 2014 were associated with a higher parasitaemia risk. This result is expected since malaria is a vector-borne disease sensitive to changes in climatic conditions (Snow et al., 2015). Temperature influences the speed of development of mosquitoes and *Plasmodium* parasites (Gullan and Cranston, 2014). Rainfall is the most important driver of mosquito population dynamics and malaria transmission because it provides the optimal humidity and medium for mosquito fertilization and breeding (Githeko and Ndegwa, 2001a; Kynast-Wolf et al., 2006).

Although a reduction in parasitaemia risk was achieved in all regions, nevertheless, parasitaemia risk was still high in the regions of North East, West Nile, and East Central compared to other regions. This disproportionately high risk in these regions in spite of the high intervention coverage might be attributed to low socio-economic development (Ministry of Finance, 2014), and limited access to health services (Yeka, 2012). In the case of East Central region, rice growing practiced in this region has been documented as a potential driver of malaria risk transmission due to the large swamps that provide a favorable habitat for mosquito breeding (Pullan et al., 2010). Similarly, other studies have reported a higher malaria risk in settings with low socio-economic status (Protopopoff et al., 2009), poor access to health services (Tanner and de Savigny, 2008), and rice paddies (Diboulo et al., 2016).

The strong reduction in the estimated number malaria-infected children may also underline the effect of increases in interventions coverage (Uganda Bureau of Statistics and ICF International, 2015), urbanization (Kigozi et al., 2015), and generally improving socio-economic conditions (Tusting et al., 2016).

3.5 Conclusions

Our study demonstrates that malaria control interventions have had a strong effect on the decline of parasitaemia risk in Uganda during 2009-2014, albeit with varying magnitude in

the regions. This success should be sustained by optimizing ITN coverage to achieve universal coverage and by timely replacing worn-out ITNs. NMCP should sustain the malaria prevention awareness campaigns through the use of Information, Education, and Communication (IEC) materials to further promote the use of ITNs. In the high burden districts where IRS implementation is on-going, efforts should be made to ensure that all households are sprayed periodically every six months.

NMCP should address the problems limiting ACTs coverage scale-up by providing free RDTs to all healthcare providers in line with the WHO 'Test and Treat' campaign, and increasing supervision for private health facilities.

The varying intervention effects in different regions may be an indication that interventions work differently in different regions of the country. This, therefore, calls for a better understanding of the environmental and entomological conditions in each region to tailor a combination of interventions suitable to local settings that will have a maximum reduction on transmission.

Also, in the regions where the risk remains disproportionately high, NMCP needs to conduct specific studies to understand human and/or vector behavior responsible for this problem. In these regions, other tools should be introduced such as chemoprevention especially in the high-risk group of children less than 5 years and mass drug administration to reduce the parasite load in the population. In order to maximize intervention effects and avert reversal in malaria risk reduction, government, and donor-funded poverty reduction programs should prioritize regions/districts where socio-economic conditions are low.

In summary, the ambitious targets of UMRSP 2014-2020 can be achieved if the country commits to implementing an integrated package to cover all aspects of disease prevention, management, and health. However, this will only be possible if the current funding portfolio is increased from the contemporary less than $1 average per head per year to

the recommended $4 per head per year (Teklehaimanot et al., 2007) which is equivalent to $140million per year.

Abbreviations

ACTs: Artemisinin Combination Therapies; MIS: Malaria Indicator Surveys; ITNs: Insecticide Treated Nets; IRS: Indoor Residual Spraying; WHO: World Health Organization; UMRSP: Uganda Malaria Reduction Strategic Plan (UMRSP); SSA: Sub-Saharan Africa; PMI: President's Malaria Initiative; MoH: Ministry of Health; NMCP: National Malaria Control Program; GRUMP: Global Rural-Urban Mapping Project; RS: Remote Sensing; LST: Land Surface Temperature; NDVI: Normalized Difference Vegetation Index; MODIS: Moderate Resolution Imaging Spectroradiometer; EWES: Environmental Monitoring System; BCI: Bayesian credible intervals; DHS: Demographic health survey.

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Declarations

Ethics approval and consent to participate

In this study we analyzed secondary data made available by the Demographic Health Survey (DHS) MEASURE. According to survey protocols and related documents of the two surveys, ethical approval was obtained from the Institutional Review Board of International Consulting Firm (ICF) of Calverton, Maryland, USA, and also from Makerere University School of Biomedical Sciences Higher Degrees Research and Ethics committee (SBS-HDREC), and the Uganda National Council for Science and Technology (UNCST). Details of ethical clearance are published in the Uganda MIS 2009 and MIS 2014–15 reports for the first and second survey, respectively [9, 10].

Consent for publication

Not applicable.

Availability of data and materials

The DHS MEASURE program prohibits researchers from redistributing data as per their "Dataset Terms of Use". However, the data are available in the DHS MEASURE program website (www.dhsprogram.com) upon request following data access instructions (http://dhsprogram.com/data/Access-Instructions.cfm). Also, data can be requested through the following contact; Tel: (301) 572–0851, E-mail: archive@dhsprogram.com.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

JS developed methodology, analyzed and synthesized data, fitted models, carried out data validation, and wrote the manuscript; BN participated in data analysis and synthesis; JK carried out data curation and participated in manuscript writing; BA carried out data curation and participated in manuscript writing; FM formulated research goals and objectives, participated in the process of acquisition of project financial support, and manuscript writing; SK formulated research goals and objectives, planned, coordinated, and executed research, and manuscript writing; PV formulated research goals and objectives, planned, coordinated, and executed research, spearheaded study methodology development, and manuscript writing. All authors read and approved the final manuscript.

3.6 Appendix

Statistical modeling details

A1. Estimating parasitaemia risk at two survey time periods

A geostatistical model was developed to assess the effect of environmental/climatic factors on parasitaemia risk for the first survey. Let $Y_1(s_i)$ be the number of children less than 5 years who tested positive in cluster s_i in the first survey, and $N_1(s_i)$, the total number of children tested. We assume that $Y_1(s_i)$ follows a Binomial distribution, that is, $Y_1(s_i)|N_1(s_i), \pi_1(s_i) \sim \text{Bin}(N_1(s_i), \pi_1(s_i))$ $\forall i \in 1,\ldots,n_1$, where $\mathbf{s}=\{s_1, s_2,\ldots,s_n\}$ is the set of locations surveyed, $s_i \subset R^2$ and $\pi_1(.)$ indicates the parasitaemia risk. A Bayesian geostatistical model to analyze parasitaemia risk was formulated as follows:

$\text{logit}(\pi_1(s_i)) = \boldsymbol{\beta_1^T X_1}(s_i) + \omega_1(s_i)$, where $\mathbf{X_1}(s_i)$ is the set of environmental/climatic predictors at location s_i, $\boldsymbol{\beta_1} = (\beta_{11}, \beta_{12}, \ldots, \beta_{1k})^T$ is the vector of regression coefficients and $\boldsymbol{\omega_1} = (\omega_1(s_1), \omega_1(s_2), \ldots, \omega_1(s_{n1}))^T$ is a zero-mean latent spatial process that follows a multivariate normal distribution, that is, $\boldsymbol{\omega_1} \sim \text{MVN}(0, \sigma_1^2 R_1)$. R_1 is the correlation matrix defined by an exponential parametric function of the distance d_{ij} between two location s_i and s_j that is, $R(s_i, s_j) = \exp(-d_{ij}\rho_1)$. The parameter σ_1^2 is the spatial variation and ρ_1 is a smoothing parameter that controls the rate of correlation decay with increasing distance. The range parameter was calculated by the ratio $\frac{3}{\rho_1}$ to estimate the minimum distance beyond which spatial correlation is negligible (<5%). Following standard formulation of Bayesian regression models, we assumed vague priors; an inverse-gamma for σ_1^2, a gamma prior distributions for ρ_1, and non-informative Gaussian distributions with mean 0 and variance 10^2 for the regression coefficients. Thus, $\sigma_1^2 \sim$IG(0.01,0.01), $\rho_1 \sim$Gamma(2.01,1.01), $\beta_{1k} \sim$N(0, 10^2), k=1,…,K.

To produce a smooth map, Bayesian kriging was employed to predict parasitaemia risk at unsampled locations on a 2x2 km^2 grid using the predictive posterior distribution, $p(\mathbf{Y_0}|\ \mathbf{Y}) = \int p(\mathbf{Y_0}|\boldsymbol{\beta_1}, \boldsymbol{\omega}_0)p(\boldsymbol{\omega}_0|\boldsymbol{\omega}_1, \sigma_1^2, \rho_1)p\left(\boldsymbol{\beta_1},\ \boldsymbol{\omega}_1, \rho_1, \sigma_1^2\middle|Y_1(s_i)\right)d\boldsymbol{\beta_1}d\boldsymbol{\omega}_0d\boldsymbol{\omega}_1d\sigma_1^2d\rho_1$, where $\mathbf{Y_0}=(Y_1(s_{01}), Y_1(s_{02}), \dots, Y_1(s_{0l}))^T$ is the number of infected children at unsampled location $\mathbf{s_0} = \{s_{01}, s_{02}, \dots, s_{0l}\}$, $\boldsymbol{\omega}_0$ is the spatial random effect at $\mathbf{s_0}$. The distribution of $\boldsymbol{\omega}_0$ given $\boldsymbol{\omega}_1$ is multivariate normal, that is, $p(\boldsymbol{\omega}_0|\boldsymbol{\omega}_1, \sigma_1^2, \rho_1)$ =MVN $(R_{01}R_{11}^{-1}U, \sigma_1^2(R_{01} - R_{01}R_{11}^{-1}R_{10}))$, with R_{11}=cor$(\boldsymbol{\omega}_1, \boldsymbol{\omega}_1)$, $R_{01} = R_{10}^T$ = cor$(\boldsymbol{\omega}_0, \boldsymbol{\omega})$ and $p(Y(s_{0i})|\boldsymbol{\beta_1}, \boldsymbol{\omega}(s_{0i}))$~ Bin$(Y(s_{0i}), \pi_0(s_{0i}))$, and thus logit $(\pi_0(s_{0i}))= \boldsymbol{\beta_1}^T\mathbf{X}(s_{0i}) + \boldsymbol{\omega}(s_{0i})$. For mapping purposes, predictions were made for 52,794 pixels covering a regular grid of Uganda.

Using a geostatistical model similar to the one described above, estimates of malaria risk were obtained for the second survey. Similarly, a binomial distribution was assumed for the number of positive children $Y_2(s_i')$, that is, $Y_2(s_i')|N_2(s_i'), \pi_2(s_i')$~Bin$\left(N_2(s_i'), \pi_2(s_i')\right)$, $\forall i \in 1, \dots, n_2$ where $\mathbf{s}' = \{s_1', s_2', \dots, s_{n_2}'\}$ is the set of locations sampled in the second survey, which is different from $\mathbf{s}$. $\pi_2(s_i')$ was modeled as a function of the environmental factors and a spatial process $\boldsymbol{\omega_2}$, that is, $\boldsymbol{\omega_2}$~MVN$(0, \sigma_2^2R_2)$ with spatial variance σ_2^2 and scaling parameter ρ_2. On the logit scale, this takes the form, $\text{logit}\left(\pi_2(s_i')\right) = \boldsymbol{\beta_2^T}\mathbf{X_2}(s_i') + \omega_2(s_i')$. Also, prediction of parasitaemia risk for the second survey was carried out using the 2x2 km^2 resolution grid described above.

A2. Modeling the effects of interventions on the change of parasitaemia risk

The change of parasitaemia risk was modeled on the logit scale as a function of the difference in climatic conditions between the two survey times, the effect of intervention coverage, the socio-economic status and area type in the second survey, that is; $\text{logit}(\pi_2(s_i') = Z(s'_i) + \boldsymbol{\beta}(\mathbf{X_2}(s_i') - \mathbf{X_1}(s_i'))^T + \alpha_1\text{ITN}(s_i') + \alpha_2\text{IRS}(s_i') + \alpha_3\text{ACT}(s_i') + \gamma_1\text{Area}(s_i') + \gamma_2\text{wealth}(s_i') + \omega_c(s_i'))$,

where $Z(s'_i) = \text{logit}(\pi_1(s_i'))$, $ITN(s'_i)$ is the coverage indicator identified through a variable selection procedure among six ITN use and ITN ownership indicators, $IRS(s'_i)$ represents the proportion of sprayed households in cluster s'_i, $ACT(s'_i)$ is the proportion of fevers treated with any ACT, and $\boldsymbol{\omega_c}(s'_i)$ corresponds to the latent spatial process, that is, $\boldsymbol{\omega_c} \sim MVN(0, \sigma_c^2 R_c)$ with spatial variance σ_c^2. The coefficients α_1, α_2 and α_3 measure the effect of interventions on the change in parasitaemia risk, thus, $\exp(\alpha_1)$, $\exp(\alpha_2)$ and $\exp(\alpha_3)$ are the expected change in odds of parasitaemia (second survey versus first survey) associated with a 1% increase in the coverage of ITNs, IRS and ACT, respectively. $Area(s'_i)$ is a binary variable indicating whether s'_i is an urban or rural cluster, and $wealth(s'_i)$ is the median wealth score of cluster s'_i. Coefficients γ_1 and γ_2 are covariate effects quantifying the effect of $Area(s'_i)$ and $wealth(s'_i)$ on the parasitaemia odds reduction. $\boldsymbol{\omega_c(s')}$ are spatial random effects modeled by a Gaussian process as $\boldsymbol{\omega_c} \sim MVN(0, \sigma_c^2 R_c)$

We assume an inverse gamma prior distribution for σ_c^2, a gamma distribution for the parameter ρ_c, and normal priors for the regression coefficients $\boldsymbol{\beta}$, α_1, α_2, α_3, γ_1, γ_2.

Parasitaemia risk during the first survey $\pi_1(.)$ was not directly available at locations $\mathbf{s}'$ of the second survey. We addressed this spatial misalignment problem by predicting parasitaemia risk during the first period at the locations of the second survey using the Bayesian kriging. The estimation error of parasitaemia prediction was taken into account in the modeling as a measurement error in the covariate.

The joint posterior distribution of the parameters was obtained by

$$p(\boldsymbol{\beta}, \boldsymbol{\beta}_1, Z(s'), \alpha_1, \alpha_2, \alpha_3, \gamma_1, \gamma_2, \boldsymbol{\omega}_1(s), \boldsymbol{\omega_1}, \omega_c, \sigma_c^2, \rho_c, \sigma_1^2, \rho_1 | Y_2(s')) \propto$$

$$p(Y_2(s')|Z(s'), \boldsymbol{\beta}, \alpha_1, \alpha_2, \alpha_3, \gamma_1, \gamma_2, \omega_c) p(Z(s')|\boldsymbol{\beta}_1, \boldsymbol{\omega}_1) p(\boldsymbol{\omega}_1|\boldsymbol{\omega}_1) p(\boldsymbol{\omega}_1|\sigma_1^2, \rho_1) p(\boldsymbol{\omega_c}|\sigma_c^2, \rho_c) p(\boldsymbol{\beta}) p(\boldsymbol{\beta}_1)$$

$$p(\alpha_1) p(\alpha_2) p(\alpha_3) p(\gamma_1) p(\gamma_2) p(\sigma_1^2) p(\rho_1) p(\sigma_c^2) p(\rho_c)$$

A3. Spatially varying interventions effects

In order to estimate the intervention effects at regional level and account for potential interactions with endemicity levels, a second model was fitted in which we estimated intervention effects at regional level. The model was expressed as;

$$\text{logit}\left(\pi_2(s_i')\right) = Z(s_i') + \boldsymbol{\beta}\left(\mathbf{X_2}(s_i') - \mathbf{X_1}(s_i')\right) + \alpha_1\left(A_{s_i'}\right)\text{ITN}(s_i') + \alpha_2(A_{s_i'})\text{IRS}(s_i') + \alpha_3\left(A_{s_i'}\right)\text{ACT}(s_i') + \omega_c(s_i').$$

The effects of interventions are defined at regional level and denoted as $\alpha_k\left(A_{s_i'}\right), (k = 1,2,3)$ where $A_{s_i'}$ is the region where s_i' falls. Each $\alpha_k(A_i)$ was written as the sum of a conditional autoregressive effect that takes into account the similarity of the effects across the regions and an independent random component, that is, $\alpha_k(A_i) = \alpha_k^c(A_i) + \varepsilon_k(A_i)$, where $p(\alpha_k^c(A_i)|\alpha_k^c(A_j), i \neq j, \tau_{kc}) \equiv N(\frac{1}{n_i}\sum_{i\sim j}\alpha_k^c\left(A_j\right), \frac{\sigma_{kc}^2}{n_i})$ with i~j indicates the A_j areas neighboring A_i , and $\varepsilon_k(A_i) \sim N(0, \sigma_\varepsilon^2)$.

A4. Bayesian variable selection

To choose the most important ITN coverage indicator and functional form that explains the maximum variation in parasitaemia odds change, Bayesian variable selection using stochastic search was implemented. For each ITN coverage covariate X_p, a categorical indicator parameter I_p was introduced to represent exclusion of the variable from the model $(I_p = 0)$, inclusion in linear $(I_p = 1)$ or categorical $(I_p = 2)$ forms. I_p has a probability mass function $\prod_{j=0}^{2}\pi_j^{\delta_j(I_p)}$, where π_j denotes the inclusion probabilities of functional form j (j=0,1,2) so that $\sum_{j=0}^{2}\pi_j = 1$ and $\delta_j(.)$ is the Dirac function, $\delta_j(I_p) = \begin{cases}1, & \text{if } I_p = j\\ 0, & \text{if } I_p \neq j\end{cases}$. A spike and slab prior distribution was assumed for the regression coefficients. In particular for the coefficient β_p of the corresponding variable X_p in linear form, we assumed $\beta_p \sim \delta_1(I_p)N(0, \tau_p^2) + \left(1 - \delta_1(I_p)\right)N(0, \vartheta_0\tau_p^2)$ that is a non-informative prior for β_p if X_p is included in the model

in linear form (slab) and an informative normal prior shrinking β_p to zero (spike) if X_p is excluded from the model, setting ϑ_0 to be a large number, e.g, 10^5. Likewise, for the coefficients $\{\beta_{p,l}\}_{l=1,..,L}$ corresponding to the categorical form of X_p with L categories, $\beta_{p,l} \sim \delta_2(I_p)N(0, \tau_{p,l}^2) + (1-\delta_2)N(0, \vartheta_0\tau_{p,l}^2)$ was assumed. For inclusion probabilities, a non-informative Dirichlet distribution was adopted with hyper parameter $\alpha = (1,1,1)^T$, that is, $\boldsymbol{\pi} = (\pi_0, \pi_1, \pi_2)^T \sim \text{Dirichlet}(3, \alpha)$. We also assumed inverse Gamma priors for the precision hyper parameters τ_p^2 and $\tau_{p,l}^2$, $l = 1, \ldots, L$.

Joint posterior distributions

A1. Estimating parasitaemia risk at first survey

$p(\boldsymbol{\beta_1}, \boldsymbol{\omega_1}, \rho_1, \sigma_1^2 | \mathbf{Y_1}) \propto L(\boldsymbol{\beta_1}, \boldsymbol{\omega_1}, \rho_1, \sigma_1^2; \mathbf{Y_1})\ p(\boldsymbol{\beta_1})\ p(\boldsymbol{\omega_1} | \sigma_1^2, \rho_1)\ p(\sigma_1^2)\ p(\rho_1)$, where $L(\boldsymbol{\beta_1}, \boldsymbol{\omega_1}, \rho_1, \sigma_1^2; \mathbf{Y_1})$ is the likelihood, $p(\boldsymbol{\beta_1})$, $p(\boldsymbol{\omega_1} | \sigma_1^2, \rho_1)$, $p(\sigma_1^2)$ and $p(\rho_1)$ are prior distributions of regression parameters, spatial random effects, variance and correlation parameters, respectively.

$p(\boldsymbol{\beta_1}, \boldsymbol{\omega}_1, \rho_1, \sigma_1^2 | \mathbf{Y_1}) \propto \prod_{i=1}^{n1} \pi_1(s_i)^{\mathbf{Y_1}} (1 - \pi_1(s_i)^{n1 - \mathbf{Y_1}}) \det(R_1)^{-1} \exp(-\frac{1}{2} \rho_1{}^T R_1^{-1} \rho_1) (\sigma_1^2)^{-(a+1)} \exp(-\frac{b}{\sigma_1^2})$, where $\pi_1(s_i) = \frac{\exp(\boldsymbol{\beta_1^T X_1}(s_i) + \omega_1(s_i))}{1 + \exp(\boldsymbol{\beta_1^T X_1}(s_i) + \omega_1(s_i))}$

A1. Estimating parasitaemia risk at second survey

$p(\boldsymbol{\beta_2}, \boldsymbol{\omega}_2, \rho_2, \sigma_2^2 | \mathbf{Y_2}) \propto L(\boldsymbol{\beta_2}, \boldsymbol{\omega}_2, \rho_2, \sigma_2^2; \mathbf{Y_2})\ p(\boldsymbol{\beta_2})\ p(\boldsymbol{\omega}_2 | \sigma_2^2, \rho_2)\ p(\sigma_2^2)\ p(\rho_2)$, where $L(\boldsymbol{\beta_2}, \rho_2, \sigma_2^2; \mathbf{Y_2})$ is the likelihood, and $p(\boldsymbol{\beta_2})$, $p(\boldsymbol{\omega}_2 | \sigma_2^2, \rho_2)$, $p(\sigma_2^2)$ and $p(\rho_2)$ are the prior distributions of regression parameters, spatial random effects, variance and correlation parameters, respectively.

$p(\boldsymbol{\beta_2}, \boldsymbol{\omega}_2, \rho_2, \sigma_2^2 | \mathbf{Y_2}) \propto \prod_{i=1}^{n2} \pi_2(s_i)^{\mathbf{Y_2}} (1 - \pi_2(s_i)^{n2 - \mathbf{Y_2}}) \det(R_2)^{-1} \exp(-\frac{1}{2} \rho_2{}^T R_2^{-1} \rho_2) (\sigma_2^2)^{-(a+1)} \exp(-\frac{b}{\sigma_2^2})$, where $\pi_2(s_i) = \frac{\exp(\boldsymbol{\beta_2^T X_1}(s_i) + \omega_2(s_i))}{1 + \exp(\boldsymbol{\beta_2^T X_2}(s_i) + \omega_2(s_i))}$

A2. Modeling the effects of interventions on the change of parasitaemia risk

$$p(\boldsymbol{\beta}, \boldsymbol{\beta}_1, Z(s'), \alpha_1, \alpha_2, \alpha_3, \gamma_1, \gamma_2, \omega_c(s'), \boldsymbol{\omega}_1(s), \boldsymbol{\omega}_1(s'), \boldsymbol{\omega}_c, \sigma_c^2, \rho_c, \sigma_1^2, \rho_1 | Y_2(s')) \propto$$

$$p(Y_2(s') | \boldsymbol{\beta}, \alpha_1, \alpha_2, \alpha_3, \gamma_1, \gamma_2, Z(s'), \omega_c(s')) p(Z(s') | \boldsymbol{\beta}_1, \boldsymbol{\omega}_1(s')) p(\boldsymbol{\omega}_1(s') | \boldsymbol{\omega}_1(s)) p(\boldsymbol{\omega}_1(s) | \sigma_1^2, \rho_1)$$

$$p(\omega_c(s') | \sigma_c^2, \rho_c) p(\boldsymbol{\beta}) p(\boldsymbol{\beta}_1) p(\alpha_1) p(\alpha_2) p(\alpha_3) p(\gamma_1) p(\gamma_2) p(\sigma_1^2) p(\rho_1) p(\sigma_c^2) p(\rho_c)$$

A3. Spatially varying interventions effects

$$p(\boldsymbol{\beta}, \boldsymbol{\beta}_1, Z(s'), \boldsymbol{\alpha_1}(A_{s'}), \boldsymbol{\alpha_2}(A_{s'}), \boldsymbol{\alpha_3}(A_{s'}), \boldsymbol{\omega_c}(s'), \boldsymbol{\omega}_1(s), \boldsymbol{\omega_1}(s'), \boldsymbol{\omega_c}, \sigma_{k_c}^2, \rho_c, \sigma_1^2, \rho_1 | Y_2(s')) \propto$$
$$p(Y_2(s') | \boldsymbol{\beta}, \boldsymbol{\alpha_1}(A_{s'}), \boldsymbol{\alpha_2}(A_{s'}), \boldsymbol{\alpha_3}(A_{s'}), Z(s'), \boldsymbol{\omega_c}(s')) p(Z(s') | \boldsymbol{\beta}_1, \boldsymbol{\omega}_1(s')) p(\boldsymbol{\omega}_1(s') | \boldsymbol{\omega}_1(s))$$

$$p(\boldsymbol{\omega_1}(s) | \sigma_1^2, \rho_1) p(\boldsymbol{\omega_c}(s') | \sigma_{k_c}^2, \rho_c) p(\boldsymbol{\beta}) p(\boldsymbol{\beta}_1) p(\boldsymbol{\alpha_1}(A_{s'})) p(\boldsymbol{\alpha_2}(A_{s'})) p(\boldsymbol{\alpha_3}(A_{s'})) p(\sigma_1^2) p(\rho_1) p$$
$$(\sigma_{k_c}^2) p(\rho_c)$$

Prior distributions for model parameters were assumed as in A2 above except for the spatially varying interventions effects $\alpha_k(A_{s'})$ for which a CAR prior distribution was adopted, implying that each $\alpha_k(A_i)$ conditional on $\alpha_k(A_j)$ follows a normal distribution with mean equal to the average of neighboring regions A_j and variance inversely proportional to the number of neighbor regions n_i, that is $p(\alpha_k(A_i) | \alpha_k(A_j), i \neq j, \tau_{kc}) \sim N\left(\frac{1}{n_i} \sum_{i \sim j} \alpha_k(A_j), \frac{\sigma_{kc}^2}{n_i}\right)$.

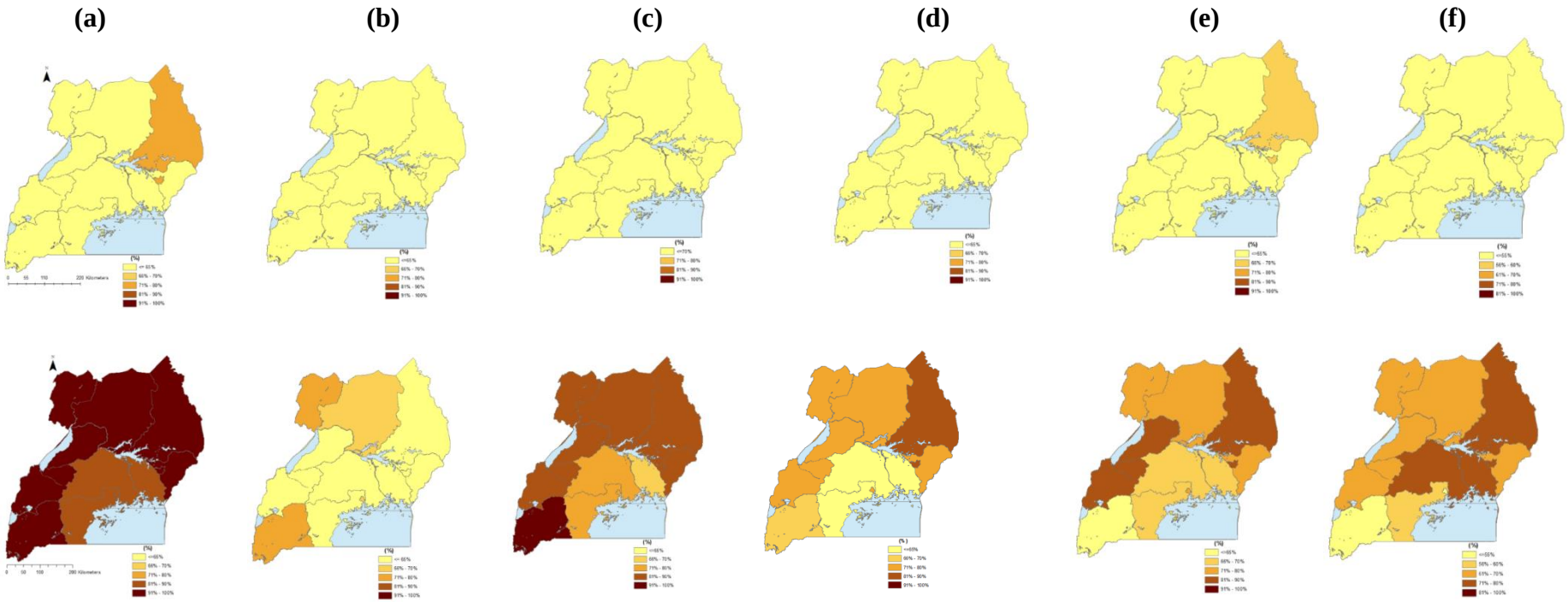

Figure 3.6: Malaria intervention coverage in 2009 and 2014; (a) Percentage of households with one ITN, (b) percentage of households with at least 1 ITN for every two people, (c) percentage of population with access to an ITN, (d) percentage of population that slept under an ITN the previous night, (e) percentage of children less than 5 years who slept under an ITN the previous night, (f) proportion of fever episodes treated with any ACT (f)

Chapter 4: The effects of case management and vector-control interventions on space-time patterns of malaria incidence in Uganda

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Abstract

Background

Electronic reporting of routine health facility data in Uganda began with the adoption of the District Health Information Software System version 2 (DHIS2) in 2011. This has improved health facility reporting and overall data quality. In this study, the effects of case management with artemisinin-based combination therapy (ACT) and vector control interventions on space-time patterns of disease incidence were determined using DHIS2 data reported during 2013-2016.

Methods

Bayesian spatio-temporal negative binomial models were fitted on district-aggregated monthly malaria cases, reported by two age groups, defined by a cut-off age of 5 years. The effects of interventions were adjusted for socio-economic and climatic factors. Spatial and temporal correlations were taken into account by assuming a conditional autoregressive (CAR) and a first-order autoregressive AR(1) process on district and monthly specific random effects, respectively. Fourier trigonometric functions were incorporated in the models to take into account seasonal fluctuations in malaria transmission.

Results

The temporal variation in incidence was similar in both age groups and depicted a steady decline up to February 2014, followed by an increase from March 2015 onwards. The trends were characterized by a strong bi-annual seasonal pattern with two peaks during May-July and September-December. Average monthly incidence in children < 5 years declined from 74.7 cases (95%CI: 72.4-77.1) in 2013 to 49.4 (95%CI: 42.9-55.8) per 1000 in 2015 and followed by an increase in 2016 of up to 51.3 (95%CI: 42.9-55.8). In individuals ≥5 years, a decline in incidence from 2013 to 2015 was followed by an increase in 2016. A 100% increase in insecticide-treated nets (ITN) coverage was associated with a decline in incidence by 44%

(95%BCI: 28-59%). Similarly, a 100% increase in ACT coverage reduces incidence by 28% (95%BCI: 11-45%) and 25% (95%BCI: 20-28%) in children < 5 years and individuals ≥5 years, respectively. The ITN effect was not statistically important in older individuals. The space-time patterns of malaria incidence in children < 5 are similar to those of parasitaemia risk predicted from the malaria indicator survey (MIS) of 2014-15.

Conclusion

The decline in malaria incidence highlights the effectiveness of vector-control interventions and case management with ACT in Uganda. This calls for optimizing and sustaining interventions to achieve universal coverage and curb reverses in malaria decline.

Key words: artemisinin-based combination therapy (ACT), Bayesian inference, Conditional Auto regressive (CAR) model, District Health Information Software System version 2 (DHIS2), malaria interventions, insecticide treated nets (ITN), Negative binomial

4.1 Introduction

The launch of the Roll Back Malaria (RBM) programme and the Global Fund to Fight AIDS, Tuberculosis and Malaria marked the first serious international efforts to control and prevent malaria in sub-Saharan Africa (SSA), since the global malaria eradication programme was abandoned in the 1970s (Snow and Marsh, 2010). These efforts have accelerated the scale-up of vector control interventions and case management with artemisinin-based combination therapy (ACT) in endemic countries leading to a significant decline in malaria morbidity and mortality (Bhatt et al., 2015a). In spite of this success, malaria still remains a public health problem in the majority of countries in SSA with the heaviest burden borne in children less than 5 years old (World Health Organization, 2016).

In Uganda, the scaling-up of interventions resulted in the decline of malaria parasitaemia risk during 2009-2015 (Ssempiira et al., 2017a, 2017b), but nonetheless, the country still ranks among the top six high burdened in the world (National Malaria Control Program, 2016).

The Uganda Health Management Information System (HMIS) was established in the early 1990s to facilitate reporting of routine health facility data to the Ministry of Health (MoH) (Kintu et al., 2004). The system has since undergone several revisions and multiple technological upgrades to strengthen health facility and district-based reporting and improve reporting of routine health facility data. The most crucial improvement was the adoption of the District Health Information Software System version 2 (DHIS2) in 2011 which facilitated the transition from a paper-based reporting and storage to an electronic web-based system in 2011.

To ensure a fast and effective roll-out process, the Ministry of Health (MoH) with support from international partners conducted 35 regional training workshops during January 2011-January 2012 for all district records assistants, Biostatisticians, health officers and

HMIS focal persons. By July 2012, all districts were using DHIS2 online and reporting monthly HMIS data, thanks to the strong IT capacity of the MoH staff, technical and financial support from CDC and USAID. In spite of some challenges in the beginning, such as internet connectivity issues and limited workforce there was a great improvement in health reporting after the introduction of DHIS2 in 2012/13 compared to the period before 2012. Completeness and timeliness of outpatient reporting increased from 36% and 22% in 2011/12 to 85% and 77% in 2012/13, respectively. Also, most child-related health coverage indicators increased from about 50% in 2011/12 to over 80% in 2012/13 (Kiberu et al., 2014).

However, routine health facility data utilization in Uganda remains low and disease burden estimation relies mainly on population-based surveys such as the Demographic Health Survey (DHS) and Malaria Indicator Survey (MIS) (Bain et al., 1997). MIS are conducted periodically every five years to estimate malaria parasite prevalence in children less than five years (Uganda Bureau of Statistics and ICF International, 2015, 2010). The DHIS2 data, on the other hand, provides an opportunity to investigate inter and intra-annual variation of malaria risk in individuals for all age groups presenting with malaria to health facilities. The adoption of 'Test and Treat' campaign by MoH has greatly improved the number of health facility malaria cases confirmed by the Rapid Diagnostic Tests (RDTs) (National Malaria Control Program, 2016). This data can provide a wealth of information for monitoring and evaluation of malaria programming activities to support evidence-based decision making.

Routine health facility data are spatially and temporally correlated due to common exposures in proximal areas and time points. Bayesian Conditional Autoregressive (CAR) models adjust for spatial correlation in district-level incidence and smooth disease rates to highlight the spatial pattern of the true burden and produce unbiased parameter estimates (Carsten et al., 2007). Bayesian space-time CAR models have been applied to analyze malaria cases routinely collected from health facilities in Namibia (Alegana et al., 2013),Venezuela

(Villalta et al., 2013), Mozambique (Zacarias and Andersson, 2011), Malawi (Kazembe, 2007), Zimbabwe (Mabaso et al., 2006), China (Clements et al., 2009) and in South Africa (Kleinschmidt et al., 2002). These studies investigated effects of environmental and socio-economic factors on inter and intra annual variation of malaria incidence.

In this work, Bayesian negative binomial CAR models were fitted on district-aggregated monthly malaria cases reported in the DHIS2 during 2013-2016 to estimate the effects of malaria interventions on the spatio-temporal patterns of the disease incidence in Uganda in children less than 5 years and individuals of 5 years and above. The models were adjusted for climatic and socio-economic factors. The results provide important information to National Malaria Control Programme (NMCP) for evaluating progress and for planning the timing and priority areas to allocate malaria interventions.

4.2 Methods

4.2.1 Settings

Uganda is located in East Africa on a large plateau in the great lakes region. Its altitude varies between 1,300–1,500 m above sea level and the mean annual temperature ranges from 16°C to 30°C. It has a diverse vegetation, mainly comprising of tropical rainforests in the South, wooded savanna in Central, and semi-arid in the North and North East regions. There are two rainy seasons; the first during March-May and the second from August to November. The population is 37 million, of which 18% are children < 5 years (Uganda Bureau of Statistics, 2016). The country is divided into 112 districts and covers an area of 241,039 square kilometers.

Malaria transmission rates are among the highest in the world (Talisuna et al., 2015). Transmission is stable in 95% of the country. Low and unstable transmission is mainly present in the highland areas. Malaria is responsible for 33% of outpatient visits and 30% of hospitalized cases. *Anopheles gambiae sensu lato (s.l.)* is the dominant vector species

followed by *Anopheles funestus*, which is commonly found in areas having permanent water bodies with emergent vegetation. These two vectors are strongly endophilic and endophagic that is, feeding indoors and resting on walls after feeding, which makes vector control approaches effective. Health facilities in Uganda are classified and graded according to their service scope and size of the population they serve in the following (descending) order; hospitals, Health Center (HC) IVs, HCIIIs and HCIIs. At the time of conducting this study, there were 5,418 health facilities; 160 hospitals, 197 HCIVs, 1,289 HCIIIs and 3,772 HCIIs.

4.2.2 Data sources

4.2.2.1 Malaria cases

Data on confirmed malaria cases by RDT was extracted from the DHIS2 covering the period of January 2013 to December 2016. The data were reported by two age groups: children < 5 years and individuals ≥ 5 years. Malaria incidence in each age group was estimated by dividing the district aggregated malaria cases by the district age group-specific population. The populations for 2013, 2015 and 2016 were estimated using the national housing and population census of 2014 adjusted for the annual population growth rate (Uganda Bureau of Statistics, 2016).

4.2.2.2 Malaria interventions, socio-economic and climate data

Malaria interventions data, that is, Insecticide Treated Nets (ITNs) and case management with Artemisinin Combination Therapies (ACTs) were obtained from the MIS 2014-15 (Uganda Bureau of Statistics and ICF International, 2015). Indoor Residual Spraying (IRS) was not included in the analysis because of its sparse distribution in the majority of the districts owing to the targeted implementation strategy used in its deployment (National Malaria Control Program, 2016).

Six ITN coverage indicators were defined from the MIS 2014-15; corresponding to three ownership and three use indicators defined by Roll Back Malaria (RBM) namely;

proportion of households with at least one ITN, proportion of households with at least one ITN for every two people, proportion of population with access to an ITN in their household, proportion of the population that slept under an ITN the previous night, proportion of children under five years old who slept under an ITN the previous night, proportion of existing ITNs used the previous night.

Also, the wealth score computed from household possessions captured in the MIS 2014-15 questionnaires was used as a socio-economic proxy. A wealth index of five quintiles was generated from the score based on the data distribution following the DHS methodology (Vyas and Kumaranayake, 2006). Environmental and climatic data were downloaded from remote sensing sources during October 2012-August 2016. Day and night Land Surface Temperature (LST), Normalized Difference Vegetation Index (NDVI), and land cover were extracted from Moderate Resolution Imaging Spectroradiometer (MODIS) at a spatial resolution of 1 x 1 km^2 and temporal resolution of 8 days, 16 days and annually, respectively. Dekadal rainfall data was obtained from the US early warning and environmental monitoring system at 8 x 8 km^2 resolution. Altitude was extracted from the shuttle radar topographic mission using the digital elevation model. We used the ESRI's ArcGIS 10.2.1 to estimate distances between major water bodies and district centroids (http://www.esri.com/).

4.2.3 Statistical analysis

The analysis was carried out separately for each age group, i.e. children < 5 and individuals ≥ 5 years old. Time series plots were employed to describe inter and intra-annual variation of malaria incidence and temporal variation of environmental/climatic factors during the study period.

Biological considerations of the malaria transmission cycle suggest that there is an elapsing period between climatic suitability for malaria transmission and occurrence of cases, which is related to climatic effects on the duration of the sporogony cycle i.e. the development

of the parasite within the mosquito (Teklehaimanot et al., 2004a). We took this into account by creating lagged variables for the time varying climatic predictors (i.e. rainfall, NDVI, day LST and night LST). In particular, three analysis variables were constructed for each climatic factor by averaging its values over the following periods: the current and the previous month (lag1), the current and the two previous months (lag2) and the current and the three previous months (lag3). Categorical variables were generated based on tertiles of the variables' distributions since the relationship between malaria and environmental predictors is not always linear (Bayoh and Lindsay, 2003).

Bayesian spatio-temporal negative binomial models were fitted on the incidence data. Heterogeneity in incidence was taken into account via year-specific, spatially structured and unstructured random effects modeled at district level via CAR and Gaussian exchangeable prior distributions, respectively (Banerjee and Fuentes, 2012). The nested space-time structure allowed the geographical variation of malaria to vary from year to year. Furthermore, temporal correlation across months was captured by monthly random effects modeled by an autoregressive process of order 1. Models were adjusted for seasonality by including Fourier terms as a mixture of two cycles with periods of six and 12 months, respectively (Rumisha et al., 2013). A yearly trend was fitted to estimate changes in the incidence rates over time. Bayesian variable selection implemented within the spatio-temporal model was applied to identify the most important ITN coverage indicator and lagged climatic factor with their functional form (i.e. linear or categorical). For the ITN indicators, a categorical variable was introduced into the model taking values 1 to 7, (six values corresponding to the six indicators and the seventh defined the absence of all indicators from the model). The probabilities of the above values were treated as parameters and used to estimate the likelihood of including the ITN indicator into the model, i.e. inclusion probability. Similarly, for each climatic factor, we introduced a categorical variable taking 3 values corresponding to its absence, or inclusion

into the model in linear or categorical form. An ITN indicator or climatic factor was selected when its posterior inclusion probability was above 50%.

Intervention and wealth score data from MIS, summarized at district level may not provide reliable estimates of the coverage because the survey is designed to produce reliable estimates at country and regional level. Therefore we estimated coverage at district level by fitting Bayesian CAR binomial and Gaussian models on the aggregated intervention and wealth score data, respectively.

Malaria cases seen at formal health facilities in Uganda are a fraction of the total cases due to low health seeking behavior (Ndyomugyenyi et al., 2007), therefore we adjusted the models for the proportion of malaria treatment seeking behavior reported in the most recent MIS survey (Uganda Bureau of Statistics and ICF International, 2015). However, the survey was designed to provide precise estimates of the malaria health seeking indicator at the country and regional level. Therefore we used the Conditional Autoregressive (CAR) model to obtain estimates at district-level (Banerjee and Fuentes, 2012). Modeling details are available in the Appendix.

Models were implemented in OpenBUGS (Lunn et al., 2000) and parameters were estimated using Markov chain Monte Carlo (MCMC) simulation. We run a two-chain algorithm for 200 000 iterations with an initial burn-in period of 5,000 iterations Convergence was assessed by visual inspection of trace and density plots and analytically by the Gelman and Rubin diagnostic (Raftery and Lewis, 1992). Parameters were summarized by their posterior medians and 95% Bayesian Credible Intervals (BCIs). Maps of estimated, smoothed incidence rates were produced in ESRI's ArcGIS 10.2.1 (http://www.esri.com/). Details on model formulations are provided in the Appendix.

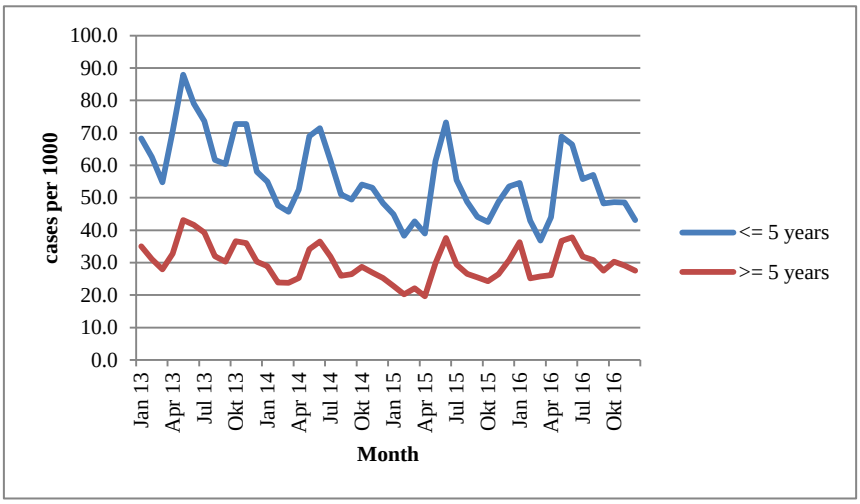
4.3 Results

The annual number of malaria cases declined from 16,475,631 in 2013 to 13,724,255 in 2014 and to 13,057,293 in 2015, but rose to 15,016,031 in 2016, representing annual declines of 16.7% and 4.9%, and an increase of 15.0%, respectively. Malaria incidence in children < 5 years during the study period (i.e. Jan 2013-December 2016) was nearly two times higher than in individuals ≥ 5 years (Figure 4.1). The average monthly incidence in children < 5 years declined steadily from 74.7 (95%CI: 72.4-77.1) in 2013 to 49.4 (95%CI: 42.9-55.8) in 2015, a decline of over 34% followed by an increase in 2016 of up to 51.3 (95%CI: 42.9-55.8). In the older age group, a steady decline in monthly incidence from 2013 to 2015 was also followed by an increase in 2016.

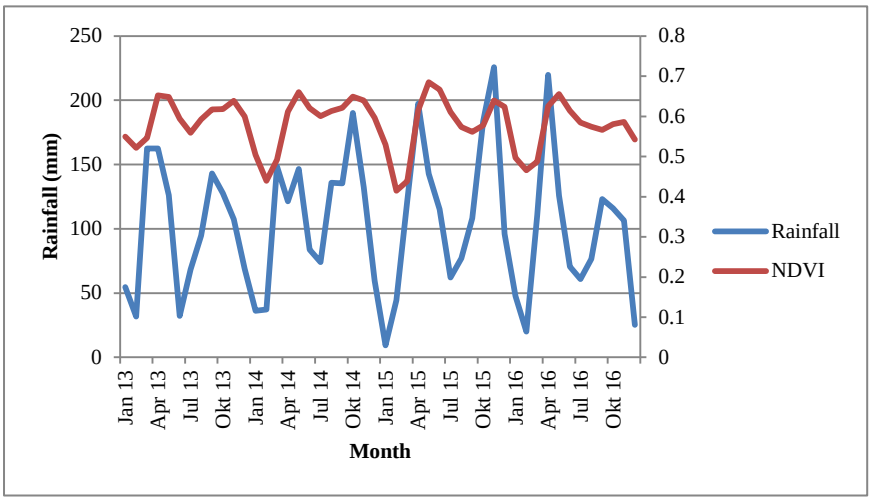
The highest malaria incidence in children < 5 years was reported in Moroto district of North East region during December 2013 (334.5 per 1000 persons) and in older individuals, the highest incidence was observed in Ntungamo district in South western region during March 2016 (282.5 per 1000 persons). Temporal trends show a strong bi-annual seasonal pattern with two peaks during May-July and September-December (Figure 4.1). The temporal variation of incidence in both age groups is highly positively correlated with that of climatic factors, but the extreme land surface temperature was negatively related to incidence.

Results from the Bayesian variable selection of the ITN coverage indicators (Table 4.1) show that the proportion of the population with access to an ITN in the household had the highest probability of inclusion among all ITN indicators. Therefore, this indicator was used as a measure of ITN coverage. Climatic averages of categorical forms of lags up to 2 months (LST, NDVI), and 3 months (rain) had higher inclusion probabilities in both age groups.

(a)



(b)



(c)

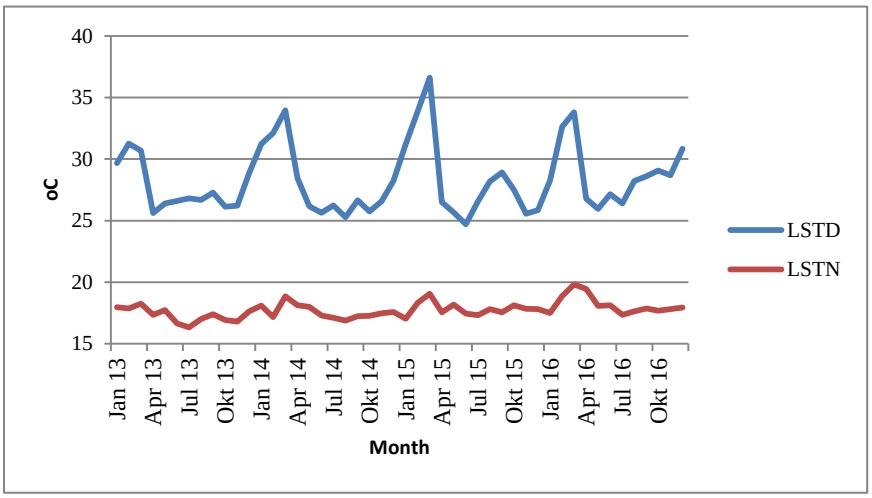


Figure 4.1: Temporal variation of monthly incidence and climatic factors during 2013-2016; a) incidence, b) Rainfall (primary axis) and NDVI (secondary axis), and c) LSTD and LSTN

Table 4.1: Posterior inclusion probabilities for ITN coverage indicators

Indicator	Probability of inclusion	
	<5 years	>=5 years
Proportion of households with at least one ITN	10.0%	10.7%
Proportion of households with at least one ITN for every two people	9.0%	11.9%
Proportion of population with access to an ITN in their household	**56.2%**	**48.5%**
Proportion of the population that slept under an ITN the previous night	2.5%	12.5%
Proportion of children under five years old who slept under an ITN the previous night	22.3%	15.2%
Proportion of existing ITNs used the previous night	0.0%	1.2%

Table 4.2 presents spatio-temporal estimates of the effects of interventions adjusted for climatic and socioeconomic confounders. These results were obtained from models with only spatial random effects which provided a better fit to the data compared to models incorporating both spatial and non-spatial heterogeneities. For instance, the Deviance Information Criterion (DIC) was 83370 and 83579 for models on children <5 years with only spatial and with both spatial and non-spatial random effects, respectively.

ITN coverage had a protective effect in children < 5 years but no statistically important effect in individuals ≥5 years. However, case management with ACT had a protective effect in both age groups. In particular, a 100% increase in the proportion of people sleeping under an ITN was associated with a decline in malaria incidence in children < 5 years of 44% (95%BCI: 28-59%). A 100% increase in the proportion of fevers treated with ACT was related with a decline in incidence of 28% (95%BCI: 11-45%) in children < 5 years and of 25% (95%BCI: 20-28%) in older individuals. Socio-economic status was an important predictor of malaria incidence in both age groups, but the effect was much stronger in the younger group. The incidence is lower in the higher socio-economic levels.

The effects of environmental and climatic factors on malaria incidence were almost similar in the two age groups. In children < 5 years, incidence increased with higher rainfall, NDVI, and day LST, but decreased with altitude. However, excessive increase in LST was associated with a statistically important decrease in incidence. Similarly, for individuals ≥5 years, incidence increased with rainfall, NDVI, and LSTD, and decreased with altitude. Land cover had no effect on malaria incidence in both age groups.

Table 4.2: Effects of interventions on malaria incidence estimated from Bayesian spatio-temporal models adjusted for socio-economic and climatic factors

Predictor	**Children less than 5 years (n=16,638,104)**	**Individuals 5 years and above (n=41,345,996)**
	IRR (95%BCI)	**IRR (95%BCI)**
Interventions[§]		
ITNs	0.56 (0.41, 0.72)*	1.08 (1.00, 1.17)
ACTs	0.72 (0.55, 0.89)*	0.75 (0.72, 0.80)*
Wealth index†		
Poorest (11,374,365)	1	1
Poorer (10,602,075)	0.87 (0.77, 0.98)*	0.88 (0.83, 1.93)
Middle (8,076,579)	0.77 (0.70, 0.84)*	0.80 (0.77, 0.84)*
Richer(12,828,925)	0.75 (0.71, 0.81)*	0.81 (0.73, 0.86)*
Richest (15,102,156)	0.79 (0.66, 0.97)*	0.84 (0.76, 0.95)
Proportion health seeking behavior	1.09 (1.07, 1.11)*	1.07 (1.04, 1.09)*
Rainfall (mm)		
<=76.9	1	1
77.0 - 125.7	1.02 (0.99, 1.05)	1.02 (0.95, 1.11)*
125.8 - 348.8	1.04 (1.01, 1.09)*	1.05 (1.01, 1.12)*
NDVI		
<=0.6	1	1
0.61-0.70	1.13 (1.09, 1.16)*	1.17 (1.14, 1.25)*
0.71-6.54	1.15 (1.12, 1.20)*	1.21 (1.17, 1.27)*
LSTD (^{0}C)		
<27.5	1	1
27.6-29.4	1.05 (1.02, 1.16)*	1.06 (1.02, 1.12)*
29.5-36.5	0.86 (0.80, 0.92)*	0.85 (0.82, 0.88)
LSTN (^{0}C)		
<18.0	1	1
18.1-18.5	0.99 (0.95, 1.02)*	0.97 (0.95, 1.05)
18.6-22.0	0.90 (0.86, 0.94)*	0.91 (0.89, 0.96)*
Altitude	0.80 (0.73, 0.88)*	0.92 (0.89, 0.94)*
% of district covered by crops	0.98 (0.91, 1.04)	1.00 (0.97, 1.02)
% of district covered by water	1.00 (0.95, 1.09)	1.00 (0.96, 1.04)
Temporal trend	***Median (95%BCI)***	***Median (95%BCI)***
2013	1	1
2014	0.002 (-0.03, 0.02)	-0.16 (-0.19, -0.14)
2015	-0.13 (-0.15, -0.09)	-0.06 (-0.12, -0.02)
2016	0.23 (0.19, 0.23)	-0.12 (-0.16, -0.10)
Amplitude		
Annual	0.33 (0.15, 0.50)	0.28 (0.16, 0.78)
Semi-annual	0.11 (0.07, 0.20)	0.15 (0.09, 0.41)
Phase (months)		
Annual	2.66 (1.51, 5.68)	2.19 (1.40, 5.63)

Predictor	**Children less than 5 years (n=16,638,104)**	**Individuals 5 years and above (n=41,345,996)**
	IRR (95%BCI)	**IRR (95%BCI)**
Semi-annual	2.09 (1.16, 5.51)	1.56 (0.87, 4.99)
Spatial variance		
2013	1.20 (0.90, 1.57)	1.21 (0.91, 1.58)
2014	1.05 (0.79, 1.37)	1.00 (0.76, 1.30)
2015	1.52 (1.14, 1.99)	1.34 (1.01, 1.75)
2016	1.16 (0.87, 1.51)	1.04 (0.78, 1.36)
Temporal variance	16.89 (10.82, 25.05)	17.20 (11.06, 25.37)
Temporal correlation	0.94 (0.83, 0.99)	0.63 (0.10, 0.93)
Dispersion	14.03 (13.47, 14.60)	16.12 (15.49, 16.77)

***** *Statistically important effect*

§ *Coverage was modeled on the scale of 0 to 1 - therefore one unit increase in coverage corresponds to a 100% increase which implies a shift of the current by 100%.*

†*Relative frequency distribution (a) < 5years; poorest (22%), poorer (20%), Middle (13.4%), Richer (19%), Richest (25.6%) (b) <=5 years; poorest (18.7%), poorer (17.6%), Middle (14.1%), Richer (23.4%), Richest (26.2%)*

Spatial variance in both age groups was highest in 2015 and lowest in 2014. In all years the spatial variability of incidence in young children was slightly higher than that of individuals ≥5 years except in 2013. However, temporal variation was much higher than spatial variability in all years. The temporal trend shows that malaria incidence in both age groups decreased during 2013 - 2015, and then increased again in 2016. The amplitude estimates suggest that malaria incidence was almost twice as high in children less than 5 years compared to older individuals. The seasonality phase parameters indicate that the peak of the malaria incidence occurs during February to May.

Maps of smoothed malaria incidence estimated from the Bayesian models are presented in Figures 4.2 and 4.3 for the first month of each quarter and study year (i.e. January, April, July, and October). The space-time patterns of incidence differ between the two age groups. The high malaria burden districts throughout the study period were located in the Northern, North West and Eastern regions. In children < 5 years, the burden of malaria was high in 2013 with the majority of the districts having incidence rates of over 50 cases per 1000 persons. The districts located in the South Western and Central regions had a much lower malaria incidence (<25 cases per 1000 persons). In 2014, incidence rates declined

except in the high burden districts of the North. Incidence declined further during the first and second quarters of 2015, reaching an overall district average of fewer than 25 cases per 1000 persons, and for the first time, the high burdened districts of North East had less than 75 cases per 1000 persons. However, starting from the third quarter of 2015 through 2016, an upsurge in incidence is apparent affecting mostly the North East region.

On the contrary, individuals ≥ 5 years had a much lower and homogeneously distributed burden throughout the country with small differences among districts. During 2013, incidence rates ranged between 25-50 cases per 1000 persons per month in most of the districts. A decline was observed through 2014 until the second quarter of 2015. Incidence started increasing at the beginning of the third quarter of 2015 up to the last quarter of 2016.It is remarkable that the spatial patterns of malaria incidence in children < 5 years during October 2014 - January 2015 bear a strong similarity with the predicted prevalence estimated from the MIS of 2014-15 which was conducted during the same period. They both indicate high burden in the regions of North East, West Nile, and East Central, and a very low burden in Kampala and South western regions.

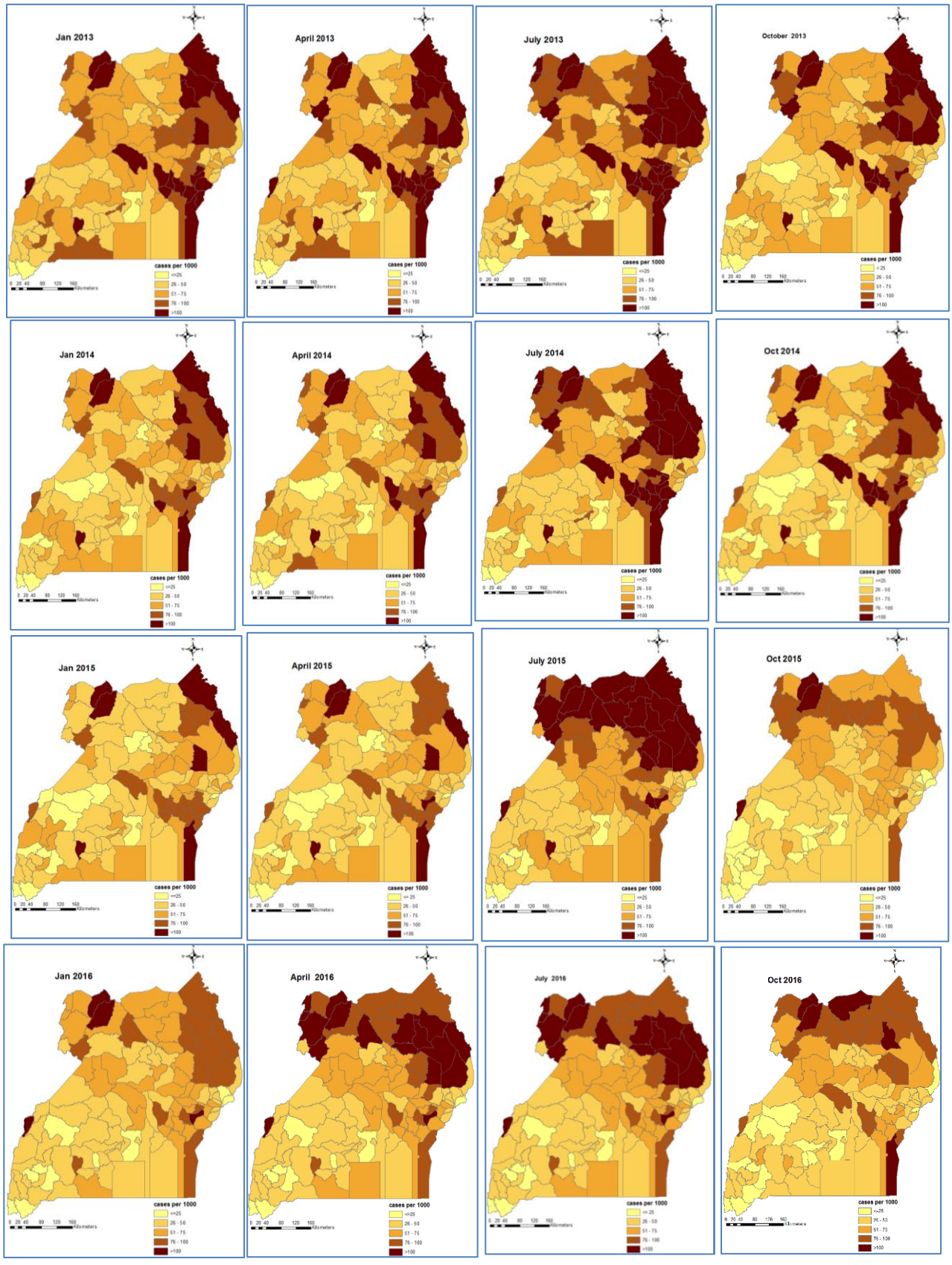


Figure 4.2: Space-time patterns of malaria incidence (cases per 1000 persons) in children less than five years estimated from the Bayesian spatio-temporal model

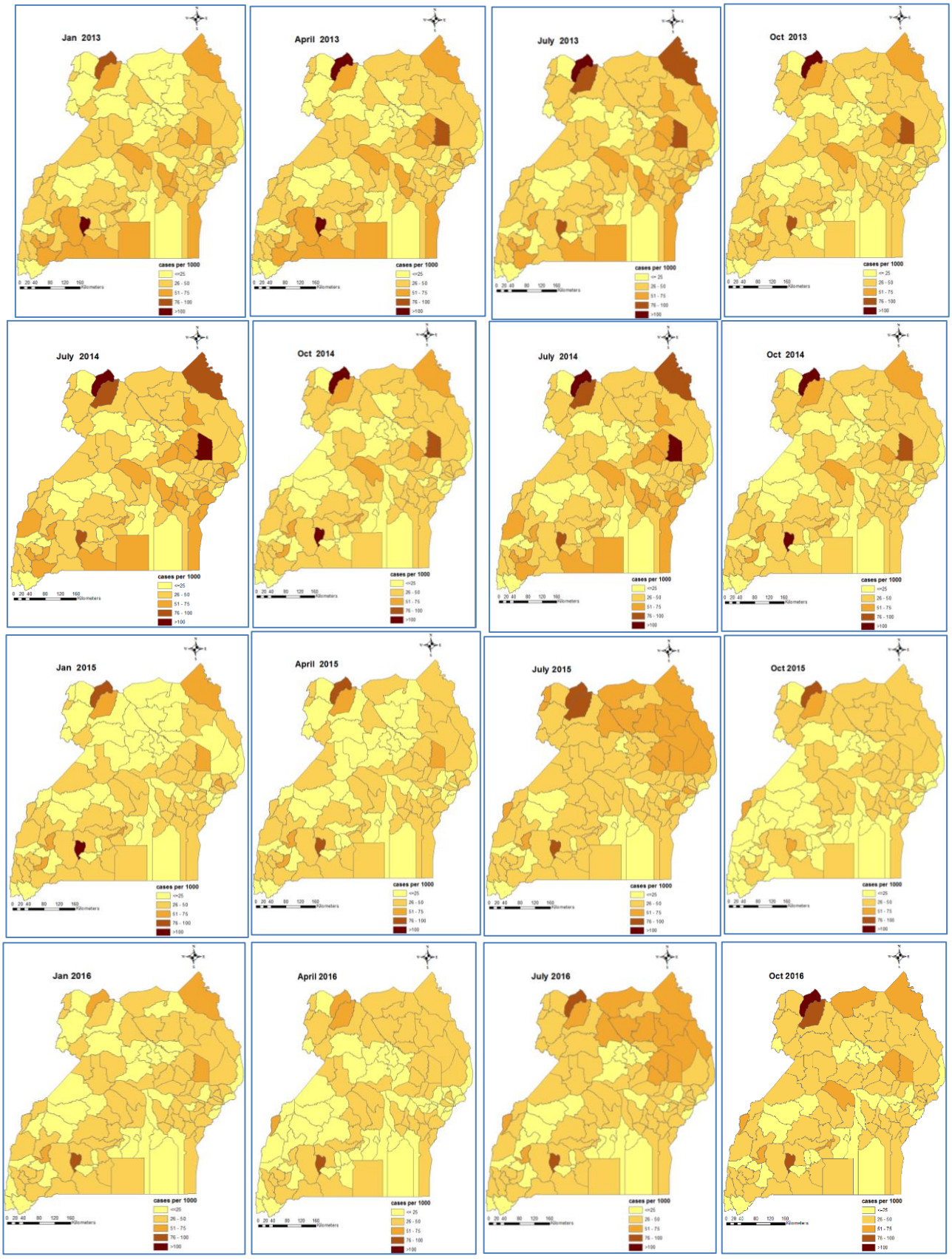


Figure 4.3: Space-time patterns of malaria incidence (cases per 1000 persons) in individuals of age five years and above estimated from the Bayesian spatio-temporal model

4.4 Discussion

In this study, the effects of ITN and case management with ACT on the space-time patterns of malaria incidence in Uganda were determined in the two age groups of below and above 5 years, using district-aggregated health facility data reported in the DHIS2 during January 2013– August 2016. Also, the smoothed space-time patterns of malaria incidence were estimated for all districts in the two age groups.

Results showed a decline in incidence between 2013 and 2014 followed by an increase in 2015. The temporal trends in the two age groups were characterized by a strong seasonal, bi-annual pattern with two peaks, at the end of the short (March-May) and longer (August-November) rainfall seasons, respectively. This result underlines the influence of rainfall patterns on inter and intra-annual variation of malaria burden in Uganda. The decline of malaria in children less than 5 years during 2013-2014 has been also shown in the analyses of the malaria indicator survey data of 2009 and 2014 (Ssempiira et al., 2017b).

A protective effect was estimated for ITNs coverage in children less than 5 years and for ACTs in both age groups. Unexpectedly the ITN effect in older individuals was statistically not important, a result that may reflect that most ITN distribution campaigns are targeting children under 5 (National Malaria Control Program, 2016) and young children have different sleeping patterns compared to adults. Young children tend to go to bed early and therefore are less exposed to mosquito bites if they sleep under an ITN unlike adults who usually sleep late (Stevenson et al., 2012). However, some studies have reported no differences in ITN use between children and adults (Bejon et al., 2009; Buchwald et al., 2017). The effectiveness of ITNs in young children derives from the endophagic nature of the *Anopheles gambiae* vector which feeds indoors where ITNs physically deter the vector from sucking a blood meal thus interrupting transmission between human and vector (Sutcliffe and

Yin, 2014). Our findings agree with results reported from population surveys in Uganda (Ssempiira et al., 2017a, 2017b), and in other endemic settings (Bhatt et al., 2015a).

Similarly, the effectiveness of ACTs on malaria incidence in all ages derives from their action of suppressing and killing malaria parasites in the body, thus lowering the parasite load and consequently the chances of transmission (Baird, 2008). The coverage and hence effectiveness of ACTs has been further enhanced by the current national MoH guidelines that recommend the use of ACTs and outlaw the use of other antimalarial drugs for malaria treatment in both private and public health facilities (National Malaria Control Program, 2016). Similar findings have been reported in other studies (Ssempiira et al., 2017a, 2017b).

The space-time patterns of smoothed malaria incidence revealed heterogeneously distributed the burden of high intensity in children under 5 years, but rather homogeneous spatial patterns of low intensity in older individuals. Young children have lower immunity which makes them highly susceptible to developing clinical malaria when they are bitten by infectious mosquitoes (Jenkins et al., 2015). With the development of immunity in older individuals, the risk of clinical malaria decreases (Pemberton-Ross et al., 2015) and therefore geographical patterns of malaria incidence are more homogeneous.

The increase in malaria burden observed in 2015 may suggest changing malaria transmission dynamics as a result of sustained high intervention coverage which may lead to loss of immunity as a result of lower exposure to malaria (World Health Organization, 2016). Similar increases in incidence have been reported in other endemic countries where interventions have been scaled up in recent times including Zambia, Tanzania, and Rwanda (World Health Organization, 2016). The high burden of malaria incidence in the young children reported in the districts of North East, Eastern and West Nile regions could be attributed to differences in ecological conditions, and disparities in socio-economic development, urbanization, and access to health services (Ssempiira et al., 2017a, 2017b).

Study results further showed a protective effect of socio-economic status on clinical malaria in both age groups which is stronger however in children under 5 years. Socio-economic status is a key confounder for epidemiological outcomes and it is the most important determinant of health in young children (Mutisya et al., 2015). The effect of socioeconomic status on malaria incidence is also reflected on the spatial patterns of the disease that revealed a lower burden in affluent districts such as Kampala and Wakiso, but a high burden in the socioeconomically disadvantaged districts of Moroto, Kotido, and Nakapiripirit in the North East. This finding confirms existing knowledge that higher socio-economic regions have a much smaller malaria burden compared to poverty-stricken ones (WHO and UNICEF, 2015).

Rainfall, normalized difference vegetation index, day and night land surface temperature, and attitude were significantly associated with malaria incidence in both age groups. Land surface temperature influences the survival of the mosquito vector and the duration of development of the vector and the parasite (Gullan and Cranston, 2009). The reduced risk of incidence associated with extreme day land surface temperature is due to reduced mosquito survival at high temperatures (Bayoh and Lindsay, 2003; Christiansen-Jucht et al., 2015a; Teklehaimanot et al., 2004a). These results are in agreement with findings from other studies that employed spatio-temporal analyses of routine health facility malaria data in Zimbabwe (Mabaso et al., 2006) and in Yunan Province, China (Clements et al., 2009), but slightly differ with results reported from a study in northern Malawi (Kazembe, 2007). Non-spatially structured heterogeneity was much higher than the spatially structured variability, which may imply high endemicity across the country irrespective of the geographical location. The temporal variation was higher than the spatial one in both age groups reflecting the stronger influence of seasonality in malaria transmission which is linked to climatic variability. The close relationship between malaria and climatic factors could be

exploited to develop a malaria early warning system for predicting malaria outbreaks (Cox and Abeku, 2007). Similar findings were the basis for the development of forecasting models in Burundi (Gomez-Elipe et al., 2007a), Ethiopia (Teklehaimanot et al., 2004a) and Botswana (Thomson et al., 2005a). It is interesting however to note that the seasonal pattern in malaria incidence varied across the country supporting the evidence of a complex relationship between climatic factors and malaria transmission and the need for regionally adapted forecasting models.

The space-time patterns of malaria incidence in children < 5 are similar to those of parasitaemia prevalence predicted from the MIS 2014-15 (Ssempiira et al., 2017a). This is an indication of the improved quality of routinely collected health facility data that can be attributed to the benefits of the DHIS2 implementation in Uganda (Kiberu et al., 2014).

A major limitation of the current study is the use of CAR models which are prone to estimation biases due to the ecological fallacy (Jenkins et al., 2015). This means that outcome-exposure relationships at the individual level may be different at the aggregated level. On the other hand, point process models such as log-Gaussian Cox model (Diggle et al., 2013) produce precise parameter estimates, but their application requires analysis of case locations data which is not available in the Uganda DHIS2 system. The data is instead reported in aggregate form at the catchment area of the health facility. However, the MoH has started piloting an electronic data record system - Open Medical Records Systems (OpenMRS) - with a plan to replace the current paper data collection by early 2019 (Ainebyoona, 2017). Once the roll-out is completed, individual case data will be available including locations which will enable us to repeat the analyses using point process models. The models will be fitted using the Integrated Nested Laplace Approximation (INLA) approach owing to the complexity of computations involved that would otherwise make MCMC infeasible.

4.5 Conclusions

The decline in malaria incidence during 2013-2015 highlights the success of vector-control interventions and case management with ACTs in the fight against malaria in Uganda. This calls for sustaining these prevention efforts to achieve universal coverage and curb the reverses in malaria decline observed in 2016. NMCP should speed up the scale-up of indoor residual spraying of households in the districts of North East and Eastern regions to reduce the persistently high burden of disease. The close similarity of disease patterns obtained in this study to the population-based survey estimates highlight the relevance of routinely collected data in disease burden estimation.

Declarations

Ethics approval and consent to participate

In this study we analyzed secondary health facility data reported from in the DHIS2 and made accessible by the ministry of health division of biostatistics. The ethics approval was waved because data analysis was carried out at district level with no reference to individual level identification particulars.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

JS developed methodology, analyzed and synthesized data, fitted models, carried out data validation, and wrote the manuscript; JK contributed to data curation, analysis and participated in manuscript writing; BN and CK participated in data analysis and synthesis; EM and JO provided data access rights, participated in synthesis and writing of manuscript; SK and FM formulated research goals and objectives, participated in the process of

acquisition of project financial support, and manuscript writing; PV formulated research goals and objectives, planned, coordinated, and executed research, spearheaded study methodology development, and manuscript writing, acquired funding. All authors read and approved the final manuscript.

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Abbreviations

DHIS2: District Health Information Software System version 2; ACTs: Artemisinin Combination Therapies; CAR: Conditional Autoregressive; MIS: Malaria Indicator Surveys; ITNs: Insecticide Treated Nets; IRS: Indoor Residual Spraying; RDTs; Rapid Diagnostic Tests; RBM: Roll Back Malaria, WHO: World Health Organization; UMRSP: Uganda Malaria Reduction Strategic Plan; SSA: Sub-Saharan Africa; MoH: Ministry of Health; NMCP: National Malaria Control Program; RS: Remote Sensing; LST: Land Surface Temperature; NDVI: Normalized Difference Vegetation Index; MODIS: Moderate Resolution Imaging Spectroradiometer; BCI: Bayesian credible intervals; DHS: Demographic health survey.

4.6 Appendix

Bayesian model formulation

Let Y_{it} be the number of malaria cases reported in calendar month *t=1,…,12,* year *j=1,…,4* and district $i = 1, \ldots, 112$. Y_{ijt} is assumed to follow a negative binomial distribution, $Y_{ijt} \sim NB(p_{ijt}, r)$ where $p_{ijt} = \frac{r}{r+\mu_{ijt}}$ where r is the dispersion parameter and μ_{ijt} is the average number of monthly malaria cases in the district. The model is formulated with a log link function, that is, $\log(\mu_{ijt}) = \log(N_{ijt}) + \alpha + X^T \beta + f_T(Z_j) + f_s(t) + \omega_{ij} + \theta_{ij} + \epsilon_{(j-1)*12+t}$ if both spatial and non-spatial random effects are incorporated, or $\log(\mu_{ijt}) = \log(N_{ijt}) + \alpha + X^T \beta + f_T(Z_j) + f_s(t) + \omega_{ij} + \epsilon_{(j-1)*12+t}$, if only spatial random effects are assumed.

Where N_{ijt} is the offset district-month specific population, α is the intercept, β is a vector of regression coefficients associated with the vector of predictors X_{it} (interventions, environmental, socio-economic status). $\epsilon_{(j-1)*12+t}$ are monthly random effects modeled by a first order autoregressive process with temporal variance σ_1^2, that is, $\epsilon_l \sim AR(1)$ where $\epsilon_1 \sim N\left(0, \frac{\sigma^2}{1-\rho^2}\right)$, $\epsilon_l \sim N(\rho\epsilon_{l-1}, \sigma^2), l = 2, \ldots, 43$ and the autocorrelation parameter ρ quantifies the degree of dependence between successive months. $f_T(Z_j)$ and $f_s(t)$ are parameters modeling the time trend and seasonality, $f_T(Z_j)$ describes an annual trend with the year Z treated as categorical covariateω_i is the spatial random effect for district i . The seasonal pattern $f_s(t)$ was captured by a mixture of two harmonic cycles with periods T_1 =6 and $T_1 = 12$ months, respectively, that is, $f_s(t) = \sum_{j=1}^{2} A_j \cos\left(\frac{2\pi}{T_j} t - \varphi_j\right) = \sum_{j=1}^{2}\{a_j * cos\left(\frac{2\pi}{T_j} t\right) + b_j * \sin(\frac{2\pi}{T_j} t)\}$, where t is time in months. A_j is the amplitude of the jth cycle and estimates the incidence peak by the expression $A_j = \sqrt{a_j^2 + b_j^2}$. $\varphi_j$is the phase which is

the point where the peak occurs estimated as $\varphi_j = \arctan\left(\frac{a_j}{b_j}\right)$, a_j and b_j are model parameters. The ω_{ij} are district- year specific random effects, modeled via conditional autoregressive CAR(σ_{1j}^2) processes. Each ω_{ij} conditional on the neighbor ω_{kj} follows a normal distribution with mean equal to the average of neighboring districts ω_{kj} , $k \in \delta_i$ and variance inversely proportional to the number of neighbor districts n_i, that is, $\omega_{ij}|\omega_{kj} \sim N\left(\gamma_j \sum_{k\in\delta_i} \omega_{kj}, \frac{\sigma_{2j}^2}{n_i}\right)$, where γ_j quantifies the amount of spatial correlation present in the data in year j, σ_{2j}^2 measures the spatial variance. ω_{ij} and ω_{kj} are adjacent districts in the set of all adjacent districts δ_i of district i, and n_i are the number of adjacent districts. θ_{ij} are exchangeable district-year random effects, i.e. $\theta_{ij} \sim N(0, \sigma_{2j}^2)$.

A non-informative normal prior distribution was assumed for the regression coefficients, a Gamma distribution with mean 1 and variance 100 for the parameter, r, an inverse gamma prior distribution with mean 10 and variance 100, for $\sigma_{1j}^2, \sigma_{2j}^2, \sigma^2$ and σ^2, i.e., $\sigma_{1j}^{-2}, \sigma_{2j}^{-2}, \sigma^{-2} \sim Ga(0.1, 0.001), j = 1, \ldots 4$ and a Uniform prior distribution for ρ, i.e. $\rho \sim U[-1,1]$.

Bayesian variable selection

To choose the most important ITN coverage indicator that explains the maximum variation in malaria incidence, Bayesian variable selection using stochastic search was implemented separately for ITN indicators, and environmental and climatic factors. For ITN indicators, a categorical variable X_p was introduced into the model and assigned values 1 to 7 representing exclusion of the variable from the model $(I_p = 1)$, and inclusion of the six indicators as follows; proportion of existing ITNs used the previous night $(I_p = 2)$, proportion of children under five years old who slept under an ITN the previous night $(I_p = 3)$, proportion of the population that slept under an ITN the previous night $(I_p = 4)$,

proportion of households with at least one ITN for every two people $(I_p = 5)$, proportion of households with at least one ITN $(I_p = 6)$, and proportion of population with access to an ITN in their household $(I_p = 7)$. Also, for lagged climatic predictors, a categorical variable Y_p was created with values 1 to 7 introduced into the model to represent exclusion of the variable from the model $(I_p = 1)$, and inclusion of different variables as follows; lag1 (continuous) $(I_p = 2)$, lag1 (categorical) $(I_p = 3)$, lag2 (continuous) $(I_p = 4)$, lag2 (categorical) $(I_p = 5)$, lag3 (continuous) $(I_p = 6)$ and lag3 (categorical) $(I_p = 7)$ For non-lagged climatic factors that is, altitude and distance to water bodies, a categorical variable Z_p with three values was defined representing exclusion from model $(I_p = 0)$, inclusion of continuous form $(I_p = 1)$, and inclusion of categorical form $(I_p = 2)$. In the latter scenario, I_p has a probability mass function $\prod_{j=1}^{2} \pi_j^{\delta_j(I_p)}$, where π_j denotes the inclusion probabilities of functional form j (j=1,2,3) so that $\sum_{j=1}^{3} \pi_j = 1$ and $\delta_j(.)$ is the Dirac function, $\delta_j(I_p) = \begin{cases} 1, & \text{if } I_p = j \\ 0, & \text{if } I_p \neq j \end{cases}$. A spike and slab prior distribution was assumed for the regression coefficients. In particular for the coefficient β_p of the corresponding variable X_p, we assumed $\beta_p \sim \delta_1(I_p) N(0, \tau_p^2) + \left(1 - \delta_1(I_p)\right) N(0, \vartheta_0 \tau_p^2)$, that is a non-informative prior for β_p if X_p is included in the model (slab) and an informative normal prior shrinking β_p to zero (spike) if X_p is excluded from the model, setting ϑ_0 to be a large number, e.g, 10^5. Similarly, $\beta_{p,l} \sim \delta_2(I_p) N(0, \tau_{p,l}^2) + (1 - \delta_2) N(0, \vartheta_0 \tau_{p,l}^2)$ was assumed for the scenario of selecting one out of six indicators/variables or exclusion of the variable. The coefficients $\{\beta_{p,l}\}_{l=1,..,7}$ corresponding to inclusion of X_p, p=1,…,7 in the model. For inclusion probabilities, a non-informative Dirichlet distribution was adopted with hyper parameter $\alpha = (1,1,1,1,1,1,1)^T$,

that is, $\boldsymbol{\pi} = (\pi_1, \pi_2, \pi_3, \pi_4, \pi_5, \pi_6, \pi_7)^{\mathrm{T}} \sim \mathrm{Dirichlet}(7, \alpha)$. We also assumed inverse Gamma priors for the precision hyper parameters τ_p^2 and $\tau_{p,l}^2$, $l = 1, \ldots, 7$.

Climatic data processing

The climatic data downloaded from MODIS that is, LSTD, LSTN and NDVI were available in the .hdf format - a raster data format. Data for each climatic factor and period was stored in different "granules", which are tile-shaped squares formed by borders of intersecting latitudes and longitudes on the earth surface. Uganda is covered by 4 such granules bounded by decimal latitude and longitude borders of N(4.234077), E(35.00000), S(-1.478794), and W(29.572774).Data for each climatic factor at a single period/time point consisted of 4.hdf files. The .hdf files were converted into other formats prior to extracting the values of each climatic factor for every district centroid using python scripts created by authors in ArcGIS. The conversions were carried out; i) combining granules to a single .hdf file, ii) conversion from .hdf file to. tiff file, iii) conversion from .tiff to ASCII format that can be read in statistical software such as STATA and R.

The dekadal rainfall data was available the .bil files format from the US early warning and environmental monitoring system. The .bil files formats were converted directly into ASCII files using customised python scripts.

For each district, monthly climatic factor estimates of LSTD, LSTN and NDVI were calculated using average function at the centroid. For rainfall it was the cumulative values that gave the total rainfall in the month.

The data was then reshaped from wide to long format, merged with malaria cases of a specific month and year belonging to a given district. Finally, three month lags were created for climatic data.

Estimating district-level interventions coverage, socioeconomic status, and health seeking behavior

Data for intervention coverage, wealth index and health seeking behavior were only available at regional level from the MIS 2014-15 and DHS 2016 surveys. This is because the population based surveys are designed to give precise estimates only at regional and country levels. A Conditional Autoregressive (CAR) model was developed to estimate district level estimates of formulated with a binomial distribution for intervention coverage and health seeking behavior indicators, and a Gaussian distribution for the wealth score, a measure of socioeconomic status. Slightly fewer than all the 112 districts had clusters selected in the original sample, therefore to fit the CAR models the districts with missing data were assigned a median value of the districts located within a specific region. The models were formulated as follows;

Let Y_i be the number of households that possessed at least one ITN in district $i = 1, \ldots, 112$, and N_i, the total number of households sampled and interviewed in district i. We assume that Y_i follows a Binomial distribution, that is, $Y_i|N_i, \pi(i) \sim Bin(N_i, \pi(i)) \quad \forall i = 1, \ldots, 112$, where $\pi(i)$ is the proportion of households with at least one ITN in district i. A Bayesian CAR model to estimate district-level ITN coverage was formulated as follows;

$\text{logit}(\pi(i)) = \beta_0 + \omega_i$, where β_0 is a constant, and ω_i, i=1,…,112, are modeled via a CAR process. Each ω_i conditional on the neighbor ω_j follows a normal distribution with mean equal to the average of neighboring districts ω_j and variance inversely proportional to the number of neighbor districtsn_i, that is; $\omega_i|\omega_j \sim N\left(\gamma \sum_{l \in \delta_i} \omega_j, \frac{\sigma_\omega^2}{n_i}\right)$, where γ quantifies the amount of spatial correlation present in the data, σ_ω^2 measures the spatial variance. ω_i and ω_j are adjacent districts in the set of all adjacent districts δ_i of district i, and n_i are the number of adjacent districts. Following standard formulation of Bayesian regression models, we assumed vague priors; A non-informative Gaussian distributions with mean 0 and variance

10^2 for β_0, that is, $\beta_0 \sim N(0, 10^2)$. An inverse gamma prior distribution with mean 10 and variance 100 was considered for σ_ω^2, i.e. $\sigma_\omega^{-2} \sim Ga(0.1, 0.001)$.

Similar formulations were applied for ACTs, malaria treatment seeking behavior, and household asset index, however the latter was modeled by a first stage Gaussian distribution.

Chapter 5: Interactions between climatic changes and intervention effects on malaria spatio-temporal dynamics in Uganda

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Abstract

Background

Although malaria burden in Uganda has declined since 2009 following the scale-up of interventions, the disease is still the leading cause of hospitalization and death. Transmission remains high and is driven by suitable weather conditions. There is a real concern that intervention gains may be reversed by climatic changes in the country. In this study, we investigate the effects of climate on the spatio-temporal trends of malaria incidence in Uganda during 2013–2017.

Methods

Bayesian spatio-temporal negative binomial models were fitted on district-aggregated monthly malaria cases, reported by two age groups, defined by a cut-off age of 5 years. Weather data was obtained from remote sensing sources including rainfall, day land surface temperature (LSTD) and night land surface temperature (LSTN), Normalized Difference Vegetation Index (NDVI), altitude, land cover, and distance to water bodies. Spatial and temporal correlations were taken into account by assuming a conditional autoregressive and a first-order autoregressive process on district and monthly specific random effects, respectively. Fourier trigonometric functions modeled seasonal fluctuations in malaria transmission. The effects of climatic changes on the malaria incidence changes between 2013 and 2017 were estimated by modeling the difference in time varying climatic conditions at the two time points and adjusting for the effects of intervention coverage, socio-economic status and health seeking behavior.

Results

Malaria incidence declined steadily from 2013 to 2015 and then increased in 2016. The decrease was by over 38% and 20% in children <5 years and individuals ≥5 years, respectively. Temporal trends depict a strong bi-annual seasonal pattern with two peaks

during April–June and October-December. The annual average of rainfall, LSTD and LSTN increased by 3.7mm, 2.2°C and 1.0°C, respectively, between 2013 and 2017, whereas NDVI decreased by 6.8%. On the one hand, the increase in LSTD and decrease in NDVI were associated with a reduction in the incidence decline. On the other hand, malaria interventions and treatment seeking behavior had reverse effects, that were stronger compared to the effects of climatic changes. Important interactions between interventions with NDVI and LSTD suggest a varying impact of interventions on malaria burden in different climatic conditions.

Conclusion

Climatic changes in Uganda during the last five years contributed to a favorable environment for malaria transmission, and had a detrimental effect on malaria reduction gains achieved through interventions scale-up efforts. The NMCP should create synergies with the National Meteorological Authority with an ultimate goal of developing a Malaria Early Warning System to mitigate adverse climatic change effects on malaria risk in the country.

Key words: Climatic; Malaria Early Warning System (MEWS); District Health Information Software System version 2 (DHIS2); Malaria interventions, Insecticide Treated Nets (ITNs); Negative binomial, Artemisinin-based Combination Therapies (ACTs); Bayesian inference, conditional autoregressive (CAR) model

5.1 Introduction

Malaria is the most common parasitic infection worldwide accounting for over 210 million clinical cases and almost half a million deaths annually (World Health Organisation, 2017). The global campaign rolled out by the World Health Organization in the aftermath of the collapse of the malaria eradication campaign has accelerated the scale-up of vector control interventions and case management with Artemisinin Combination Therapies (ACTs) leading to a significant decline in malaria morbidity and mortality in endemic countries during 2000–2015 (Bhatt et al., 2015a).

Nonetheless, malaria burden remains high in the sub-Saharan Africa (SSA) region, where *P. falciparum* causes the most severe clinical form of the disease (World Health Organization, 2016). Almost half a million deaths occur annually mostly in children less than 5 years old (World Health Organization, 2016).

In Uganda, malaria transmission remains very high and the disease ranks as the number one cause for hospitalization and death in the country (President's Malaria Initiative, 2017), despite the reduction in parasitaemia prevalence achieved during 2009 and 2014 (Ssempiira et al., 2017b). On the one hand, this high transmission is enabled by a suitable climate that is characterized by ample rainfall, optimal temperature and humidity that enhances mosquito breeding and survival of the vector and parasite (National Malaria Control Program, 2016). A number of field and laboratory studies are adduced to this effect. Temperature co-determines the duration of parasite development within the vector, larval development time and vector survival (Tanser et al., 2003). Optimum temperature range between 28°C and 32°C (Christiansen-Jucht et al., 2015a). Very low (<17°C) or high (>35°C) temperatures slow down the development of the vector or increase its mortality (Bayoh and Lindsay, 2003). On the other hand, rainfall contributes to the formation and continuation of mosquito breeding sites, thus to the increase of the vector population (Thomson et al., 2017).

Immature stages of the vector, i.e., eggs, larvae and pupae are aquatic forms and require suitable aquatic environments in which they develop prior to the emergence of adults from the pupae. Adult mosquitoes are dependent on moisture, as they are predisposed to dehydration in dry conditions having a direct negative effect on their survival (Christiansen-Jucht et al., 2015a).

Therefore, changes in temperature and rainfall are likely to affect the natural habitats of mosquitoes, alter the density of the vector while potentially exposing previously low endemic settings to malaria (Tanser et al., 2003). In Uganda, the occurrence of extreme weather conditions in the recent past such as long droughts and flooding has had an immediate impact on malaria transmission resulting in aberrations from the normal seasonal pattern in affected areas (Cox et al., 2007; Lindblade et al., 1999). Whether this short-term variability has had long-term ramifications in the country is not yet established. For effective and sustainable long-term malaria programming, it is important to investigate the potential effects of climate changes on malaria burden in consideration of the climate sensitivity of vector and parasite, and the ubiquitous human-induced global warming.

A number of studies employing either mechanistic or statistical modeling frameworks have investigated climatic change effects on the distribution and intensity of malaria risk in different settings, but have yielded dissimilar results. In some studies, a linkage was established between climatic change and the exacerbation of the risk [167–171], while in others the climatic effect was not established and instead the increasing malaria burden was attributed to other factors such as drug resistance, failure of vector control operations and changes in land use (Hay et al., 2002). Interpretations of findings from studies that employed a statistical modeling framework are often limited by the absence of good quality data stemming from the weak and fragmented nature of national health information systems in malaria-endemic countries (Yeka et al., 2012).

The Uganda Health Management Information System (HMIS) was established in the early 1990s to facilitate reporting of routine health facility data to the Ministry of Health (MoH). The system was upgraded from a paper-based reporting and storage system to an electronic web-based system in 2011 giving way to the District Health Information Software System version 2 (DHIS2) (Kiberu et al., 2014). As a result of this development, health facility data completeness and timeliness increased from 36% and 22% to more than 85% and 77%, respectively (Kiberu et al., 2014). This routine data provide an opportunity to investigate inter and intra-annual variation of malaria risk in the country and provides a wealth of information for monitoring and evaluation of malaria programming activities to support evidence-based decision making. The country's adoption of 'Test and Treat' campaign is helping to increase the number of health facility malaria cases confirmed by the rapid diagnostic tests (RDTs) (National Malaria Control Program, 2016).

Our study investigates the effects of climatic factors on the spatio-temporal patterns of malaria incidence in Uganda during 2013–2017 and assesses the relationship between climatic changes and changes in malaria incidence between 2013 and 2017 taking into account the coverage of control interventions, socio-economic factors, and malaria treatment seeking behavior patterns. Bayesian spatio-temporal negative binomial conditional autoregressive (CAR) models were fitted on district-aggregated monthly malaria cases reported in the DHIS2. Our results provide important information to National Malaria Control Programme (NMCP) for evidence-based decision making in malaria control programming in view of changing climatic conditions to sustain achieved gains and achieve elimination.

5.2 Materials and methods

5.2.1 Settings

Uganda is located in East Africa on a large plateau in the Great Lakes region. Its altitude varies between 1,300–1,500 m above sea level, and the mean annual temperature ranges from

16°C to 30°C. It has a diverse vegetation, mainly comprising of tropical rain forests in the South, wooded savanna in Central, and semi-arid in the North and North East regions. There are two rainy seasons; the first during March–May and the second from August to November. The population is 37 million, of which 18% are children < 5 years (Uganda Bureau of Statistics, 2016). The country is divided into 112 districts and covers an area of 241,039 square kilometers.

Malaria transmission rates are some of the highest in the world (Talisuna et al., 2015). Transmission is stable in 95% of the country. Low and unstable transmission is mainly present in the highland areas (>2500m) (Ministry of Health, 2014). Malaria is responsible for 33% of outpatient visits and 30% of hospitalized cases. *Anopheles gambiae s.l.* is the dominant vector species followed by *Anopheles funestus* which is commonly found in areas having permanent water bodies with emergent vegetation. These two vectors are strongly endophagic and endophilic that is, feeding indoors and resting on walls after feeding, which makes indoor vector control approaches effective. Health facilities in Uganda are classified and graded according to their service scope and size of population they serve in the following (descending) order; hospitals, Health Center (HC) IVs, HCIIIs and HCIIs. By December 2017, there were a total of 5,418 health facilities; 160 hospitals, 197 HCIVs, 1,289 HCIIIs and 3,772 HCIIs (President's Malaria Initiative, 2017).

5.2.2 Data sources

5.2.2.1 Malaria cases

Data on confirmed malaria cases by RDT was extracted from the DHIS2 covering the period of January 2013 to December 2017. The data were reported by two age groups: children < 5 years and individuals >= 5 years. Malaria incidence in each age group was estimated by dividing the district aggregated malaria cases by the district age group-specific population. The population size for each year was based on data from the national housing and population

census of 2014 adjusted for the annual population growth rate (Uganda Bureau of Statistics, 2016).

5.2.2.2 Environmental/climatic, interventions, socio-economic, and malaria treatment seeking behavior data

Environmental and climatic data were downloaded from remote sensing sources for the period October 2012–December 2017. Day Surface Temperature (LSTD) and night Land Surface Temperature (LSTN), Normalized Difference Vegetation Index (NDVI), and land cover were extracted from Moderate Resolution Imaging Spectroradiometer (MODIS) at a spatial resolution of 1 x 1 km^2 and a temporal resolution of 8 days, 16 days and annually, respectively. Dekadal rainfall data was obtained from the US early warning and environmental monitoring system at 8 x 8 km^2 resolution (Early Warning and Environmental Monitoring Program, 2016). Altitude was based on digital elevation model obtained from the Shuttle Radar Topographic Mission (SRTM). The ESRI's ArcGIS 10.2.1 software was used to estimate distances between major water bodies and district centroids (http://www.esri.com/).

Data on insecticide treated net (ITN) coverage and ACT use were obtained from the Malaria Indicator Survey (MIS) of 2014–15 (Uganda Bureau of Statistics and ICF International, 2015) and from the Uganda Demographic Health Survey (DHS) of 2016. Indoor residual spraying (IRS) was not included in the analysis because of its sparse distribution in the majority of the districts owing to the targeted implementation strategy used in its deployment (National Malaria Control Program, 2016).

Due to lack of monitoring and evaluation data outside the survey periods, we assumed that intervention coverage of 2013-14 is the same as that of 2014-15 (reported in MIS 2014-15) and the coverage of 2017 as similar to that of 2016 (available in DHS 2016). Six ITN coverage indicators were defined from the MIS 2014–15 and DHS 2016, corresponding to

three ownership and three use indicators defined by Roll Back Malaria (RBM) namely; proportion of households with at least one ITN, proportion of households with at least one ITN for every two people, proportion of population with access to an ITN in their household, proportion of the population that slept under an ITN the previous night, proportion of children under five years old who slept under an ITN the previous night, proportion of existing ITNs used the previous night. Also, the wealth score computed from household possessions captured in the MIS 2014–15 and DHS 2016 questionnaires was used as a socio-economic proxy. A wealth index of five quintiles was generated from the score following the DHS methodology (Vyas and Kumaranayake, 2006).

We also considered that malaria cases seen at formal health facilities in Uganda are a fraction of the total cases due to low health seeking behavior (Ndyomugyenyi et al., 2007). We obtained the proportion of malaria treatment seeking behavior reported in the most recent MIS survey (Uganda Bureau of Statistics and ICF International, 2015).

However, since the survey was designed to provide precise estimates at the country and regional level, we used a Bayesian CAR binomial model to obtain district-level estimates of the health-seeking behavior (Banerjee and Fuentes, 2012). Model formulation details are given in the Appendix.

5.2.3 Statistical analysis

Time series plots were employed to describe inter and intra-annual variation of malaria incidence and temporal variation of environmental and climatic factors during the study period.

Biological considerations of the malaria transmission cycle suggest that there is elapsing lag period between weather suitable for malaria transmission and occurrence of cases which is related to effects on the duration of the sporogony cycle i.e. the development of the parasite within the mosquito (Teklehaimanot et al., 2004a). We took this into account by creating

lagged variables for the time varying predictors (i.e. rainfall, NDVI, day LST and night LST). In particular, three analysis variables were constructed for each climatic factor by averaging its values over the following periods: the current and the previous month (lag1), the current and the two previous months (lag2) and the current and the three previous months (lag3). Categorical variables were generated based on tertiles of the variables' distributions since the relationship between malaria and environmental predictors is not always linear (Bayoh and Lindsay, 2003).

Bayesian spatio-temporal negative binomial models (Banerjee et al., 2014) were fitted on the incidence data. Random effects at district level were used to model spatial correlation via CAR formulations (Banerjee and Fuentes, 2012). Temporal correlation was taken into account by monthly random effects modeled by autoregressive processes. Models were adjusted for seasonality by including Fourier terms as a mixture of two cycles with periods of six and 12 months, respectively (Rumisha et al., 2013). A yearly trend was fitted to estimate changes of the incidence rates over time. Bayesian variable selection implemented within the spatio-temporal model was applied to identify the most important ITN coverage indicator and lagged climatic factors with their functional form (i.e. linear or categorical). For ITN indicators, a categorical variable was introduced into the model taking values 1 to 7, (six values corresponding to the six indicators and the seventh defining the absence of all indicators from the model). The probabilities of the above values were treated as parameters and used to estimate the inclusion probabilities of the ITN indicator into the model, i.e. inclusion probability. Similarly, for each climatic factor, we introduced a categorical variable taking three values corresponding to its absence, or inclusion into the model in linear or categorical form. An ITN indicator or climatic factor was selected if its posterior inclusion probability was above 50%.

Intervention and wealth score data from the MIS and DHS, summarized at district level, may not provide reliable estimates of the coverage because the survey is designed to produce reliable estimates at country and regional levels. Therefore, we estimated coverage at district level by fitting Bayesian CAR binomial and Gaussian models for intervention and wealth score data, respectively. The details of the model formulation are given in the appendix.

The effects of climatic changes on the decline in malaria incidence between 2013 and 2017 were modeled as a function of the difference in climatic conditions between the respective years adjusted for the effects of intervention coverage, socio-economic status and health seeking behavior in 2017.

Models were implemented in OpenBUGS (Lunn et al., 2000) and parameters were estimated using Markov chain Monte Carlo (MCMC) simulation. We ran a two-chain algorithm for 200 000 iterations with an initial burn-in period of 5,000 iterations. Convergence was assessed by visual inspection of trace and density plots and analytically by the Gelman and Rubin diagnostic (Raftery and Lewis, 1992). Parameters were summarized by their posterior medians and 95% Bayesian Credible Intervals (BCIs). Maps of estimated, smoothed incidence rates were produced in ESRI's ArcGIS 10.2.1 (http://www.esri.com/). Details on model formulations are provided in the appendix.

5.3 Results

5.3.1 Descriptive results

Overall, a total number of 71,664,624 malaria cases were reported from all health facilities during January 2013–December 2017. On annual basis, the number of reported cases declined from 16,364,773 in 2013 to 13,635,391 in 2014 and to 12,967,905 in 2015, but then increased in 2016 and 2017 to 15,016,031 and 13,680,523, respectively. This represents annual declines of 17%, 21%, 8% and 16% in 2014, 2015, 2016 and 2017, respectively compared to 2013.

Throughout the years during the study period, malaria incidence in children < 5 years was almost twice higher compared to individuals ≥5 years (Figure 5.1a).

Temporal trends of incidence in both age groups depict a strong bi-annual seasonal pattern with two peaks during April–June and October–December (Figure 1a). Similarly, climatic conditions are characterized by a bi-modal seasonality trend that is heavily influenced by the rainfall pattern marked by two rainfall seasons during March–May and August–November (Figure 5.1b).

The peaks of the rainfall seasons occur in the months of April and November for the first short and second longer season, respectively. Monthly rainfall increased from an average of 98.3mm in 2013 to 115.3mm in 2015, then decreased to 91.9mm in 2016 and increased again to 102.1mm in 2017. NDVI declined steadily from an average of 0.59 in 2013 to 0.55 in 2017, a reduction of 0.04 (6.8%).

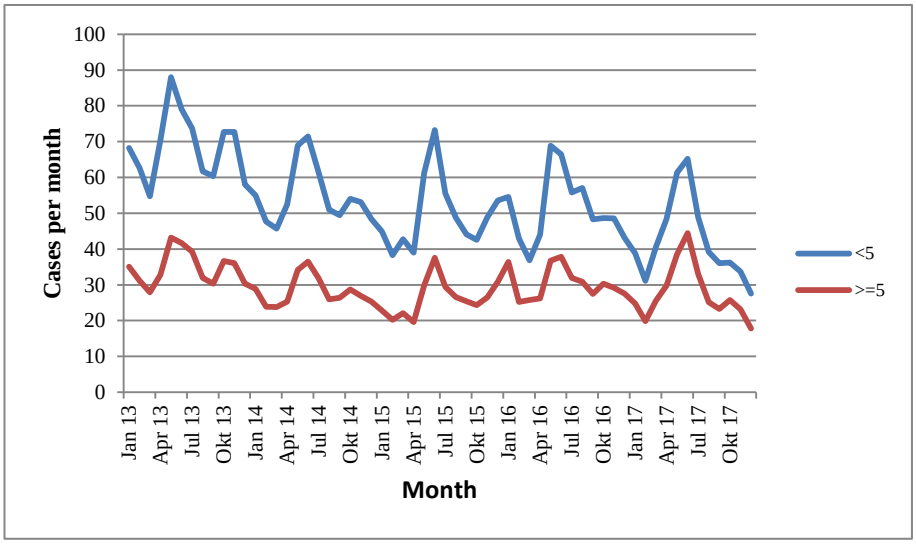
Monthly LSTD and LSTN increased steadily from an average of 27.7°C and 17.3°C in 2013 to 29.8°C and 18.3°C in 2017 –an average increase of 2.1°C and 1°C, respectively (Figure 5.1c).

The temporal variation of incidence of both age groups was closely related with that of climatic factors. Increases in land surface temperature initially favored high incidence in both age groups, but very high temperatures were followed by declines in incidence in both age groups. Also, increases and decreases in rainfall had a reciprocal though delayed influence on incidence in both age groups (Figure 5.1a).

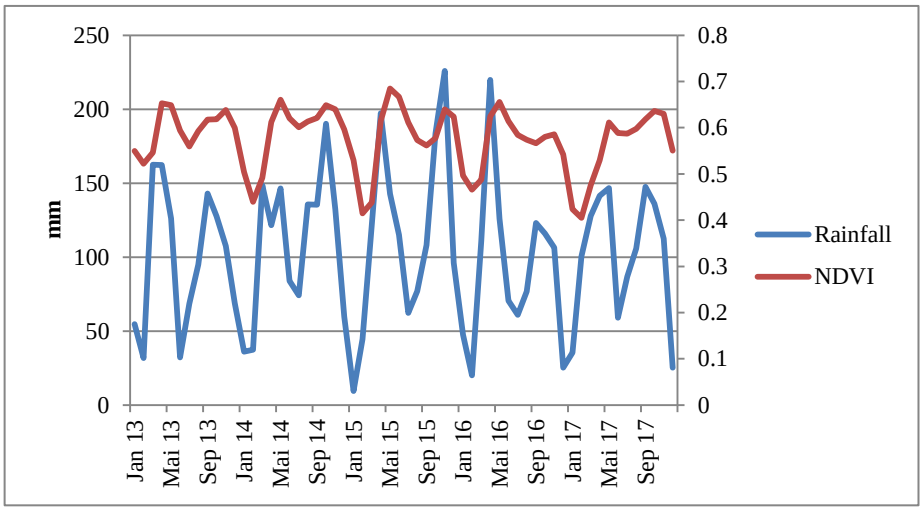
Correlation between monthly crude incidence rates and climatic averages differed in the two age groups in terms of magnitude and direction (Table 5.1). For example, malaria incidence is significantly positively correlated with rainfall of up to three months lags in children <5 years. For individuals ≥5 years, the correlation is positive, though only significant for lags of month one and month three. Correlation between incidence and NDVI for both age

groups is significantly positive for the shorter lags (months 0–2), but significantly negative for longer lags.

(a)



(b)



(c)

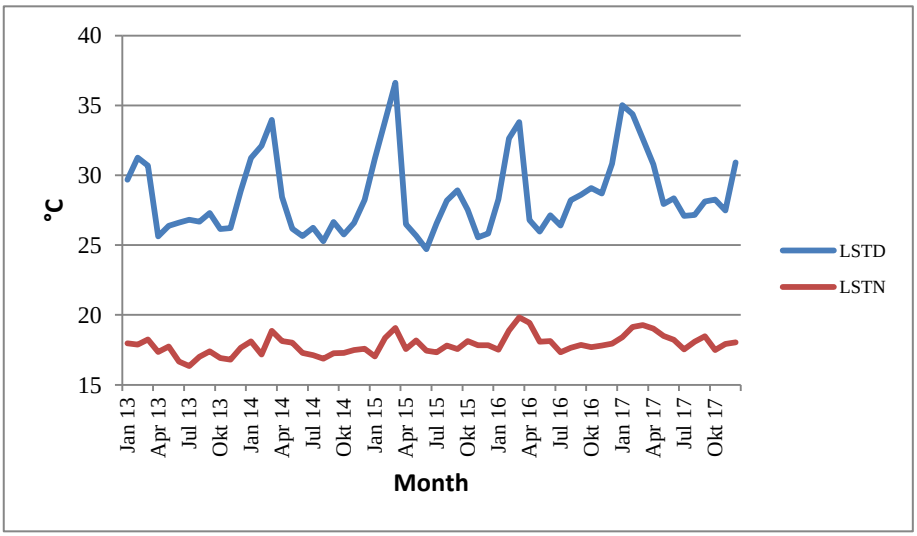


Figure 5.1: Monthly time series; (a) malaria incidence in children <5 years and individuals >= 5 years, (b) mean rainfall, (c) mean temperatures (LSTD and LSTN)

Table 5.1: Pearson correlation between mean monthly crude malaria incidence and climatic averages

Climatic factor	<5 years				>=5 years			
	Lag0	Lag1	Lag2	Lag3	Lag0	Lag1	Lag2	Lag3
Rainfall	0.05*	0.17*	0.18*	0.06*	0.01	0.14*	0.17	0.05*
LSTD	0.02	0.03*	0.14*	0.26*	-0.07*	-0.07*	0.04*	0.18*
LSTN	0.23*	0.27*	0.31*	0.33*	0.02	0.06*	0.10*	0.12*
NDVI	0.05*	0.06*	-0.01	-0.10*	0.13*	0.15*	0.08*	-0.02

*****statistically significant

5.3.2 Model-based analysis

5.3.2.1 Variable selection

Bayesian variable selection (Table 5.2) identified the same predictors for both age groups with the exception of the lag effects of rainfall. Regarding the climatic proxies with the lag effects, the highest inclusion probabilities were estimated for the categorical forms of LSTN (average of current and 3 previous months), LSTD (current and previous month), NDVI (current and 2 previous months) and rainfall (current and 3 previous months for children <5yrs; current and previous month for older individuals). Among ITN indicators, the proportion of households with at least one ITN was selected.

Table 5.2: Posterior inclusion probabilities for climatic covariates and ITN coverage indicators

Indicator	Probability of inclusion (%)	
	<5 years	>=5 years
Climatic factors		
Rainfall		
Rain_01	0.0	0.0
Rain_01*	0.0	**100.0**
Rain_012	0.0	0.0
Rain_012*	0.0	0.0
Rain_0123	0.0	0.0
Rain_0123*	**100.0**	0.0
NDVI		
NDVI_01	0.0	0.0
NDVI_01*	0.0	0.0
NDVI_012	0.0	0.0
NDVI_012*	**100.0**	**100.0**
NDVI_0123	0.0	0.0
NDVI_0123*	0.0	0.0
LSTD		
LSTD_01	0.0	0.0
LSTD_01*	**100.0**	**100.0**
LSTD_012	0.0	0.0
LSTD_012*	0.0	0.0
LSTD_0123	0.0	0.0

LSTD_0123*	0.0	0.0
LSTN		
LSTN_01	0.0	0.0
LSTN_01*	0.0	0.0
LSTN_012	0.0	0.0
LSTN_012*	0.0	0.0
LSTN_0123	0.0	0.0
LSTN_0123*	**100.0**	**100.0**
Altitude		
Altitude	**100.0**	**100.0**
Altitude*	0.0	0.0
Distance to water bodies		
Distance to water bodies	0.0	0.0
Distance to water bodies*	**100.0**	**100.0**
Interventions		
Proportion of households with at least one ITN	**100.0**	**100.0**
Proportion of households with at least one ITN for every two people	0.0	0.0
Proportion of population with access to an ITN in their household	0.0	0.0
Proportion of the population that slept under an ITN the previous night	0.0	0.0
Proportion of children under five years old who slept under an ITN the previous night	0.0	0.0
Proportion of existing ITNs used the previous night	0.0	0.0

**Categorical*
In bold: variables with highest inclusion probability that included in the final Bayesian spatio-temporal model

5.3.2.2 Effects of climatic factors on spatio-temporal changes in malaria incidence

Table 5.3 presents spatio-temporal model-based estimates of the effects of climatic factors on spatio-temporal changes in malaria incidence adjusted for interventions, socio-economic and health seeking confounders. The results were similar in both age groups. Increases in rainfall, NDVI, and LSTD were associated with an increase in malaria incidence. However, very high LSTD (above 29°C) was related with an incidence decrease. Altitude and distance to water bodies were negatively related to malaria incidence. More so, malaria burden was higher in crop cultivated areas compared to other forms of land cover.

A 100% increase in the proportion of households having at least one ITN was associated with a decline in malaria incidence in children < 5 years by 73% (95%BCI: 62–79%). The effect of ITN coverage was also protective in older individuals but not statistically important. A 100% increase in the proportion of fevers treated with ACTs was related with a reduction in incidence by 30% (95%BCI: 22–38%) in children < 5 years and by 46%

(95%BCI: 37–58%) in older individuals. Socio-economic status was an important predictor of malaria incidence in both age groups, but the effect was much stronger in the younger group. The incidence is lower in those from higher socio-economic levels. A higher proportion of malaria treatment seeking behavior was related with a reduction in spatio-temporal trends of incidence in both age groups.

Table 5.3: Effects of climatic factors on the spatio-temporal patterns of malaria incidence estimated from Bayesian negative binomial models adjusted for interventions, socio-economic and health seeking behaviour proxies

Predictor	**Children less than 5 years**	**Individuals 5 years and above**
	IRR (95%BCI)	**IRR (95%BCI)**
Rainfall (mm) (<=77.0)	1	1
77.1-126.0	1.09 (1.07, 1.13)*	1.08 (1.05, 1.10)*
126.1-354	1.13 (1.11, 1.17)*	1.09 (1.06, 1.13)*
NDVI (<=0.55)	1	1
0.56-0.66	1.13 (1.10, 1.16)*	1.18 (1.14, 1.23)*
0.67-0.81	1.19 (1.14, 1.24)*	1.28 (1.21, 1.32)*
LSTD (^{0}C) (<=26.5)	1	1
26.6-29.3	1.06 (1.03, 1.09)*	1.04 (1.01, 1.06)*
29.4-44.6	0.94 (0.88, 0.98)*	0.94 (0.92, 0.97)*
LSTN (^{0}C) **(**<=17.1**)**	1	1
17.2-18.9	1.00 (0.93, 1.11)	1.00 (0.97, 1.04)
19.0-23.3	1.00 (0.94, 1.10)	1.00 (0.95, 1.05)
Altitude	0.78 (0.72, 0.79)*	0.90 (0.86, 0.94)*
Land cover (Others)	1	1
Crops	1.07 (1.04, 1.10)*	1.10 (1.05, 1.17)*
Distance to water bodies (km)(<=16.9***)***	1	1
17.0-45.8	1.01 (0.93, 1.06)	0.87 (0.83, 0.90)*
46.0-152.6	0.86 (0.83, 0.90)	0.89 (0.80, 0.91)*
Interventions[§]		
ITNs	0.27 (0.21, 0.38)*	1.19 (1.00, 1.20)
ACTs	0.70 (0.62, 0.78)*	0.54 (0.42, 0.63)*
Interactions		
Rainfall(mm) (<=77.0)*ITNs	1	1
(77.1-126.0)*****ITNs	1.04 (0.67, 1.60)	1.19 (0.78, 1.79)
(126.1-354)*****ITNs	0.79 (0.50, 1.26)	0.82 (0.52, 1.28)
NDVI (<=0.55) *ITNs	1	1
(0.56-0.66)*ITNs	1.60 (1.03, 2.46)*	1.84 (1.21, 2.80)*
(0.67-0.81)*ITNs	3.20 (1.88, 5.43)*	3.08 (1.85, 5.13)*
LSTD (^{0}C) (<=26.5)*ITNs	1	1
(26.6-29.3)*ITNs	1.47 (1.05, 2.31)*	1.82 (1.18, 2.82)*
(29.4-44.6)* ITNs	1.70 (1.03, 2.80)*	2.46 (1.52, 3.97)*
Rainfall(mm) (<=77.0)* ACTs	1	1
(77.1-126.0)*****ACTs	1.00 (0.76, 1.30)	1.10 (0.85, 1.42)*
(126.1-354)*****ACTs	1.11 (0.82, 1.49)	1.26 (0.95, 1.67)*
NDVI (<=0.55) *ACTs	1	1
(0.56-0.66) * ACTs	1.12 (1.07, 1.48)*	1.05 (1.01, 1.37)*
(0.67-0.81) * ACTs	1.26 (1.13, 1.72)*	1.18 (1.06, 1.59)*
LSTD (^{0}C) (<=26.5) *ACTs	1	1
(26.6-29.3) * ACTs	1.18 (1.05, 1.55)*	1.37 (1.06, 1.77)*
(29.4-44.6) * ACTs	0.91 (0.68, 0.97)*	1.24 (0.92, 1.66)
Wealth index (Poorest)	1	1
Poorer	0.82 (0.77, 0.88)*	1.09 (0.99, 1.14)
Middle	0.71 (0.67, 0.74)*	0.86 (0.83, 0.90)*

Predictor	**Children less than 5 years**	**Individuals 5 years and above**
	IRR (95%BCI)	**IRR (95%BCI)**
Richer	0.70 (0.68, 0.76)*	0.83 (0.78, 0.87)*
Richest	0.78 (0.73, 0.86)*	0.91 (0.79, 0.95)*
Malaria treatment seeking behavior	0.47 (0.40, 0.53)*	0.54 (0.45, 0.60)*
Temporal trend †	***Median (95%BCI)***	***Median (95%BCI)***
2014	-0.02 (-0.03, -0.01)	-0.18 (-0.21, -0.16)
2015	-0.04 (-0.06, -0.04)	-0.39 (-0.42, -0.37)
2016	-0.03 (-0.05, -0.02)	-0.15 (-0.20, -0.10)
2017	-0.09 (-0.12, -0.07)	-0.33 (-0.40, -0.29)
Seasonal parameters		
Amplitude		
Annual	0.11 (0.04, 0.17)	0.31 (0.19, 0.36)
Semi-annual	0.14 (0.07, 0.18)	0.08 (0.03, 0.11)
Phase (months)		
Annual	2.57 (1.76, 5.90)	2.40 (1.90, 5.63)
Semi-annual	2.83 (1.19, 5.81)	1.76 (0.73, 4.64)
Spatio-temporal parameters		
Spatial variance	1.42 (1.06, 1.81)	1.27 (0.97, 1.66)
Temporal variance	18.15 (12.21, 26.06)	18.61 (12.44, 27.06)
Temporal correlation	0.94 (0.90, 0.98)	0.98 (0.95, 0.99)
Dispersion	6.84 (6.61, 7.09)	7.95 (7.68, 8.24)

***** *Statistically important effect*

† *versus 2013*

§ *Coverage was modeled on the scale of 0 to 1, therefore one unit increase in coverage corresponds to a 100% increase which implies a shift of the current by 100% .*

Results also suggested important interactions between interventions with land surface temperature and NDVI.

Temporal variation in incidence was much higher than the spatial variability. The amplitude values indicate that malaria incidence variation was almost twice as high in children less than 5 years compared to older individuals. The seasonality phase suggests that the peak of the malaria incidence occurs during February to May, in both age groups.

5.3.2.3 Space-time patterns of malaria incidence

Maps of smoothed malaria incidence estimated from the Bayesian models are presented in Figures 5.2 and 5.3 for the first month of each quarter and study year (i.e. January, April, July, and October). The high malaria burden districts throughout the study period were located in the northern and eastern Uganda. In children < 5 years, the burden of malaria was very high in 2013 with most districts having a monthly burden of more than 75 cases per 1000 persons. In 2014, a reduction in malaria burden is visible across the country with the exception of the

northern districts during the third quarter. In 2015, incidence further declined across all districts, reaching an overall district average of fewer than 55 cases per 1000 persons, and for the first time, the most of the high burdened districts in the northern region experienced a burden of fewer than 100 cases per 1000 persons. However, in 2016 a resurgence was observed, especially in the North East region. The highest reduction occurred in 2017, with the majority of the districts carrying a burden of 25-50 cases per 1000 persons.

Individuals ≥ 5 years had a much lower and a more homogeneous distributed malaria burden throughout the country with minor differences among districts. In 2013, incidence rates in individuals ≥ 5 years varied between 25–50 cases per 1000 persons per month across all districts. A decline was observed through 2014 and 2015. However, incidence rates in this age group also increased in 2016 but declined in 2017 as was the case for children less than 5 years.

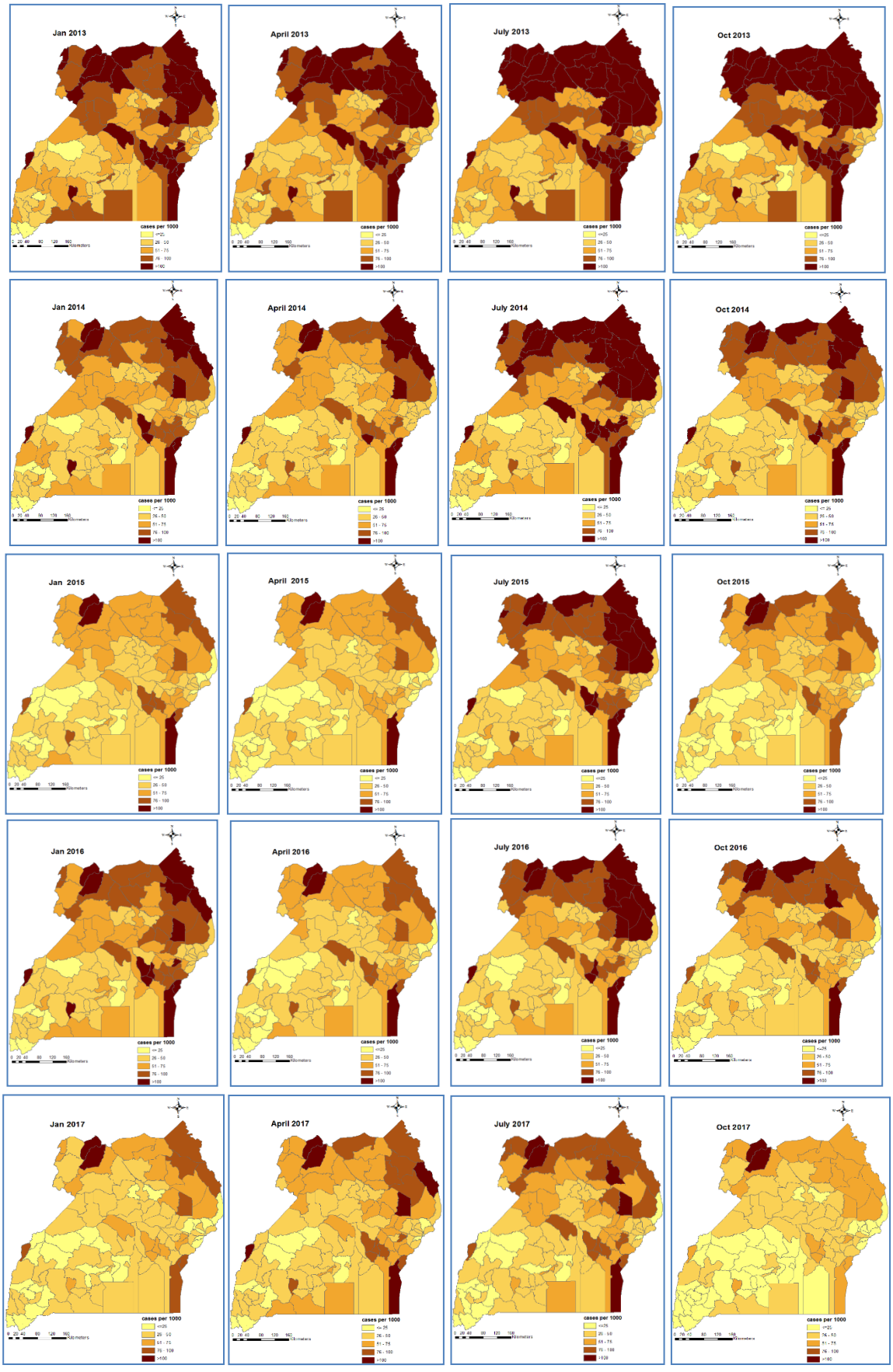


Figure 5.2: Bayesian model-based space-time patterns of malaria incidence in children <5 years

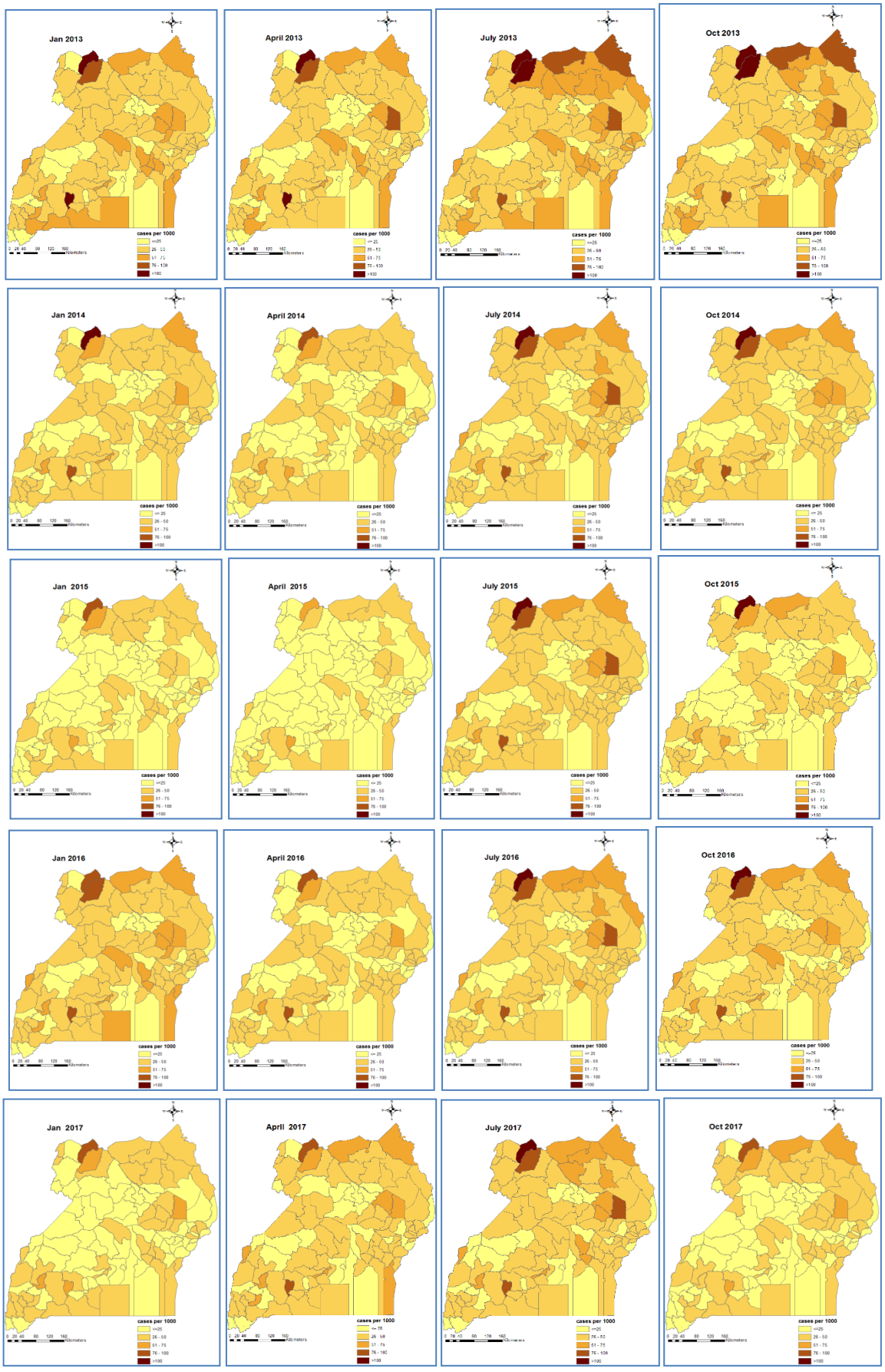


Figure 5.3: Bayesian model-based space-time patterns of malaria incidence in individuals >=5 years

5.3.2.4 Effects of climatic changes on malaria incidence decline

Table 5.4 presents estimates of the effects of climatic changes on the decline in malaria incidence between 2013 and 2017.

Malaria incidence decreased by over 38% and over 20% in children <5 years and individuals ≥5 years, respectively. In the same period, rainfall, LSTD, LSTN increased by an average of 3.7mm, 2.2°C and 1.0°C, respectively, while NDVI decreased by 6.8%. The increase in LSTD and decrease in NDVI during the study period were associated with a decrease in the reduction of malaria incidence rates in both age groups.

However, the effect of rainfall increase between 2013 and 2017 was associated with an increase in malaria incidence rates reduction, although not statistically important. The coverage of malaria interventions and the socio-economic status in 2016 (year with the most recent data) were included in the model to adjust for the effects of climatic changes. ITNs and ACTs were associated with an increase in the reduction of incidence rates of 19% (95%BCI: 18%–29%) and 78% (95%BCI: 67%–84%), respectively in children <5 years, and 34% (95%BCI: 28%–66%) and 34% (95%BCI: 28%–66%) in older individuals, respectively.

More so, higher socio-economic status and proportion of malaria treatment seeking behavior were related to a statistically important increase in the decline of malaria incidence rates across all ages.

Table 5.4: Posterior estimates for the adjusted effect of climatic changes on malaria incidence rates decline obtained from the Bayesian spatio-temporal negative binomial model

Covariate	<5 years	>=5 years
	IRR (95%BCI)	IRR (95%BCI)
Climatic changes		
Difference in rainfall	1.01 (0.98, 1.04)	1.00 (0.97, 1.03)
Difference in LSTD	0.96 (0.92, 0.98)*	0.93 (0.90, 0.96)*
Difference in LSTN	0.98 (0.96, 1.02)	0.99 (0.97, 1.02)
Difference in NDVI	0.95 (0.92, 0.98)*	0.94 (0.91, 0.98)*
Interventions		
ITN	1.20 (1.06, 1.48)*	1.79 (1.53, 1.99)*
ACTs	1.35 (1.13, 1.60)*	1.24 (1.06, 1.45)*
Proportion of malaria treatment seeking behavior	1.32 (1.12, 1.54)*	1.60 (1.39, 1.84)*
Wealth score	1.05 (1.02, 1.08)*	1.11 (1.08, 1.14)*
Other parameters		
Spatial variance	1.15 (0.86, 1.52)	1.35 (1.00, 1.81)
Temporal variation	5.27 (2.12, 10.51)	5.73 (2.54, 11.06)
Dispersion	4.91 (4.54, 5.27)	6.01 (5.58, 6.50)

**statistically important effect*

5.4 Discussion

We analyzed health facility, malaria case data, reported through the DHIS2 in Uganda to determine the effects of climatic factors on the spatio-temporal patterns of the disease and to assess the effects of climate changes on the changes in malaria incidence during 2013-2017, taking into account the effects of disease interventions.

Our findings have indicated that incidence initially declined steadily during 2013-2015 followed by a resurgence in 2016. In the same period, there was a steady increase in rainfall, day and night land surface temperature, and a steady decrease in NDVI, suggesting a more favorable environment for disease transmission. The temporal trends in incidence observed in Uganda are in line in with global malaria trends (World Health Organisation, 2017). The initial decline has been attributed to the effect of the scaled-up malaria interventions (Bhatt et al., 2015a), whereas the resurgence has been explained by insecticide resistance (Talisuna et al., 2015), migration of non-immune populations such as refugees (Coldiron et al., 2017), and by the increasing role of climate change on malaria transmission (Ngarakana-Gwasira et al., 2016).

Increases in land surface temperatures are in line with warming experienced in the past years at global and regional levels (Root et al., 2003). This increase in temperatures is consistent with observations that indicate a changing in the geographical distribution of malaria in the country beyond endemic zones to epidemic-prone due to warmer temperatures providing suitable conditions for transmission (Lindblade et al., 2000). However, a likely implication of this finding is the possible development of a stronger immunity by the naïve populations living in these areas triggered by an increased malaria exposure which will result in a reduction of fatal outcomes (Färnert et al., 2015).

The positive association observed between malaria incidence and day land surface temperature, rainfall and NDVI is in line with other studies that have demonstrated the

influence of the environment on malaria transmission (Siraj et al., 2014) and the increase of malaria transmission with temperature (Gullan and Cranston, 2014) and rainfall (Githeko and Ndegwa, 2001a; Kynast-Wolf et al., 2006). Temperature influences the survival of the mosquito vector and the duration of the development of the vector and the parasite (Gullan and Cranston, 2009). Rainfall contributes to the creation of breeding sites for mosquitoes and to an increase in humidity which favors vector development (Thomson et al., 2006). However, the relationship of malaria with rainfall is non-linear. Excess of rainfall is associated with a reduction in malaria (Lindsay et al., 2000) as it may destroy mosquito larvae (Paaijmans et al 2007) and reduce temperature (Teklehaimanot et al., 2004a).

The decline in malaria incidence is associated with extreme day land surface temperature which reduces mosquito survival (>35^{o}C) (Bayoh and Lindsay, 2003; Christiansen-Jucht et al., 2015a; Teklehaimanot et al., 2004a). The negative effect of altitude on malaria incidence is also expected since higher altitudes experience lower temperatures which make the malaria transmission slower as mosquito development cycle and the sporogony phase take much longer (Bødker et al., 2003). The inverse relationship between malaria incidence and distance to water bodies is in line with other studies that indicate a higher risk closer to breeding sites (Dlamini et al., 2015). The higher incidence of malaria in majorly cropping areas compared to forested areas may be explained by land transformation and poor agricultural practices in the former which may lead to the creation of shallow ditches and trenches that collect water when it rains and become suitable breeding sites for mosquitoes (Klinkenberg et al., 2004). These results are in agreement with findings from other studies that employed spatio-temporal analyses of routine health facility malaria data in Zimbabwe (Mabaso et al., 2006) and in Yunan Province, China (Clements et al., 2009), but differ with results reported from a study in northern Malawi (Kazembe, 2007) that reported a positive effect of altitude. Also, NDVI, a measure of vegetation is a direct response of rainfall which explains its positive relationship

with malaria incidence. A similar relationship has been described elsewhere (Liu and Chen, 2006; Midekisa et al., 2012; Thomson et al., 1999). Results of the spatio-temporal model regarding the relationship between the climatic factors and malaria incidence are confirmed by the spatial model which directly quantifies the effects of climatic changes on the decline in malaria incidence between 2013 and 2017. Other studies have also reported evidence of malaria sensitivity to climate and indicated important associations between climatic changes and malaria burden changes; in Ghana (Klutse et al., 2014), Nigeria (Weli and Efe, 2015) and Kenya (Alonso et al., 2011). Indeed in Uganda, prolonged periods of unusually high rainfall, and warmer temperatures experienced from longer drought seasons have been shown to alter the intensity, distribution, and duration of malaria transmission (Killian et al., 1999). At the global level our findings agree with those of several studies that reported a linkage between climatic change and exacerbation of malaria risk (Alonso et al., 2010; Caminade et al., 2014; Endo et al., 2017; Ermert et al., 2013), and a World Bank report indicating an increase in susceptibility to malaria as temperatures increase (International Bank for Reconstruction and Development and World Bank, Washington, DC, 2012). The implication of these finding is that malaria distribution may increase both in space and time as a result of climate change spreading to areas that previously were malaria free (Tanser et al., 2003).

The interactions of intervention effects with land surface temperature and NDVI on the spatio-temporal patterns of malaria incidence suggest a varying impact of interventions on malaria burden in different climatic conditions. This finding will inevitably call for changes in malaria programming in Uganda in view of the evidence of the changing climate.

Notably, interventions had a much stronger positive effect on the decline of malaria incidence in both age groups compared to climatic changes further underlining the importance of interventions in malaria control and their potential to mitigate adverse effects of climate change on malaria. The effectiveness of interventions in influencing malaria reduction in

Uganda is further enhanced by government policies of interventions scale-up through mass distribution of ITNs to achieve universal coverage and the formulation of guidelines supporting their smooth deployment such as one that recommends the use of ACTs for malaria treatment and prohibits the use of other antimalarial drugs in public health facilities (National Malaria Control Program, 2016). Our findings are consistent with results reported from other studies that reported a strong effect of interventions on malaria risk reduction (Bhattarai et al., 2007; Müller et al., 2006; O'Meara et al., 2010; Snow and Marsh, 2010).

More so, socio-economic status and proportion of health seeking behavior were all associated with an increase in odds of a reduction in malaria incidence. The improving socioeconomic conditions and a high rate of urbanization particularly in the central and southwestern regions coupled with an increase in health facility coverage probably explain the decline in malaria incidence and their mitigation effect on the influence of climatic change on malaria incidence during 2013-2017. The importance of socioeconomic factors on malaria burden cannot be overstated as has been shown in several studies (Feachem and Sabot, 2008; Greenwood et al., 2008; Protopopoff et al., 2009). Indeed the adverse effects of climatic factors on spatio-temporal trends of malaria incidence are highest in the northern and eastern-based districts where poverty is very high, urbanization is low and other socio-economic indicators poor (Yeka, 2012). Similarly, the disparities in malaria distribution in the most-at-risk group of children less than 5 years neither reflects that of environmental factors nor malaria interventions, but they mirror socioeconomic and health access inequalities between the north/east and south/central regions of the country (Ssempiira et al., 2017a).

A limitation in our study is the non-availability of monthly malaria interventions data and of intervention data during the years 2013 and 2017. Due to lack of monitoring and evaluation data outside the survey periods, we assumed that intervention coverage of 2013-14 is the same as that of 2014-15 (reported in MIS 2014-15) and the coverage of 2017 as similar

to that of 2016 (available in DHS 2016). Although, this assumption holds for ITNs since they have an average lifespan of three years (Ngonghala et al., 2016), it may necessarily not be true for ACTs. Furthermore, malaria transmission in Uganda is perennial, therefore we assumed that the coverage estimated from the survey data at the district level reflects the coverage for that district throughout the year. These assumptions may affect the conclusions from our findings.

5.5 Conclusions

Our study has elucidated inter and intra-annual relationships between climatic factors and malaria incidence, estimated the space-time burden of estimates, and demonstrated the effects of climatic changes on the decline of malaria incidence across all ages during 2013-2017. Malaria incidence has declined during 2013-2017, despite a major resurgence in 2016. Results have attested to a significant interplay between climatic and intervention effects and indicated that climatic factors have had a detrimental effect on malaria reduction gains achieved through accelerated interventions scale-up. To mitigate adverse climatic effects on malaria, NMCP should create synergies with the National Meteorological Authority (NMA) and harmonize interventions deployments after taking into account forecasts produced by the latter of the short-term weather and long-term climatic conditions. This should lead to the development of a Malaria Early Warning System (MEWS) to forecast malaria outbreaks in the event of adverse climatic events. Additional funding will be required for incorporating climatic mitigation plans in malaria programs, designing and operationalizing MEWS to achieve effective and sustainable malaria control in Uganda.

Acknowledgments

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5.6 Appendix

Statistical model formulation

A1. Modeling the effects of climatic factors on spatio-temporal trends of incidence

Let Y_{ijt} be the number of malaria cases reported in calendar month *t=1,…,12,* year *j=1,…,5* and district $i = 1, \ldots, 112$. Y_{ijt} is assumed to follow a negative binomial distribution, $Y_{ijt} \sim NB(p_{ijt}, r)$ where $p_{ijt} = r/(r + \mu_{ijt})$ where r is the dispersion parameter and μ_{ijt} is the average number of monthly malaria cases in the district. The model with a log link function is described below:

$\log(\mu_{ijt}) = \log(N_{ijt}) + \alpha + X^T \beta + f_T(Z_j) + f_s(t) + \epsilon_{(j-1)*12+t} + \omega_i$, where N_{ijt} is the offset district-month specific population, α is the intercept, β is a vector of regression coefficients associated with the vector of predictors X_{it} (interventions, environmental, socio-economic status). $\epsilon_{(j-1)*12+t}$ are monthly random effects modeled by a first order autoregressive process with temporal variance σ_t^2. $f_T(Z_j)$ and $f_s(t)$ are parameters modeling the time trend and seasonality, $f_T(Z_j)$ describes an annual trend with the year Z treated as categorical covariate, ω_i is the spatial random effect for district i. The seasonal pattern $f_s(t)$ was captured by a mixture of two harmonic cycles with periods T_1 =6 and $T_1 = 12$ months, respectively, that is, $f_s(t) = \sum_{j=1}^{2} A_j cos(\frac{2\pi}{T_j} t - \varphi_j) = \sum_{j=1}^{2} \{a_j * cos\left(\frac{2\pi}{T_j} t\right) + b_j * sin(\frac{2\pi}{T_j} t)\}$, where t is time in months. A_j is the amplitude of the jth cycle and estimates the incidence peak by the expression $A_j = \sqrt{(a_j^2 + b_j^2)}$. $\varphi_j$is the phase which is the point where the peak occurs estimated as $\varphi_j = \arctan(a_j/b_j)$, a_j and b_j are model parameters. ω_i, *i*=1,…,112, are modeled via a conditional autoregressive (CAR) process - each ω_i conditional on the neighbor ω_j follows a normal distribution with mean equal to the average of neighboring districts ω_j and variance inversely proportional to the number of neighbor districts n_i, that is;

$\omega_i|\omega_j \sim N\left(\gamma \sum_{l\in\delta_i}\ \omega_j, \frac{\sigma_\omega^2}{n_i}\right)$, where γ quantifies the amount of spatial correlation present in the data, σ_ω^2 measures the spatial variance. ω_i and ω_j are adjacent districts in the set of all adjacent districts δ_i of district i, and n_i are the number of adjacent districts.

Following Bayesian model formulation, prior distributions were specified for all model parameters. For the regression coefficients a non-informative normal prior distribution was assumed, a Gamma distribution with mean 1 and variance 100 was adopted for the parameter, r. ϵ_t =2, ..., 59 are error terms considered to be temporally correlated and modeled via an autoregressive process of first order i.e., $\epsilon_t \sim AR(1)$, assuming that $\epsilon_1 \sim N\left(0, \frac{\sigma^2}{1-\rho^2}\right)$ and $\epsilon_t \sim N(\rho\epsilon_{t-1}, \sigma^2), t = 2, \ldots, 59$, where ρ is the autocorrelation parameter that quantifies the degree of dependence between successive months. We assumed a Uniform prior distribution for ρ, i.e. $\rho \sim U[-1,1]$. Since the above specification conditions on the first observation, we assigned it a student t prior distribution with one degree of freedom. An inverse gamma prior distribution with mean 10 and variance 100 was considered for σ_ω^2 and σ_t^2 , i.e. $\sigma_\omega^{-2}, \sigma_t^{-2} \sim Ga(0.1, 0.001)$.

A2. Modeling the effects of climatic changes on the changes in malaria incidence

The change in malaria incidence between 2013 and 2017 was modeled on the log scale as a function of the difference in climatic conditions between the two time points, the effects of intervention coverage, socioeconomic status, and the proportion of malaria treatment seeking behavior in 2017, that is,

$\log(IR)'_{it} = \log(IR_{it}) + \boldsymbol{\beta}(\mathbf{X'_{it}} - \mathbf{X_{it}})^{\mathrm{T}} + \boldsymbol{\alpha}\boldsymbol{\Psi'_{it}} + \epsilon_t + \omega_i$, where IR_{it} and IR'_{it} are the malaria incidence rate in 2013 and 2017, respectively, $\log(IR_{it}) = \log(\mu_{it})\text{-}\log(N_{it})$, μ_{it} is the average number of monthly malaria cases in district i, and month t. $\mathbf{X_{it}}$ and $\mathbf{X'_{it}}$, are climatic covariates in 2013 and 2017 respectively and $\boldsymbol{\Psi'_{it}}$ are the non climatic covariates in 2017. The coefficients $\boldsymbol{\beta}$ and $\boldsymbol{\alpha}$ represent the magnitude of the effect associated with an increase in the

rates of decline in malaria incidence from 2013 to 2017, ϵ_t are monthly random effects modeled by a first order autoregressive process with temporal variance σ_t^2 and ω_i are spatial random effects as described in the section above.

A3. Estimating district-level interventions coverage, socioeconomic status, and health seeking behavior

Data for intervention coverage, wealth index and health seeking behavior were only available at regional level from the MIS 2014-15 and DHS 2016 surveys. This is because the population based surveys are designed to give precise estimates only at regional and country levels. A Conditional Autoregressive (CAR) model was developed to estimate district level estimates of formulated with a binomial distribution for intervention coverage and health seeking behavior indicators, and a Gaussian distribution for the wealth score, a measure of socioeconomic status. Slightly fewer than all the 112 districts had clusters selected in the original sample, therefore to fit the CAR models the districts with missing data were assigned a median value of the districts located within a specific region. The models were formulated as follows;

Let Y_i be the number of households that possessed at least one ITN in district $i = 1, \ldots, 112$, and N_i, the total number of households sampled and interviewed in district i. We assume that Y_i follows a Binomial distribution, that is, $Y_i|N_i, \pi(i) \sim Bin(N_i, \pi(i)) \quad \forall i = 1, \ldots, 112$, where $\pi(i)$ is the proportion of households with at least one ITN in district i. A Bayesian CAR model to estimate district-level ITN coverage was formulated as follows;

$\text{logit}(\pi(i)) = \beta_0 + \omega_i$, where β_0 is a constant, and ω_i, i=1,…,112, are modeled via a CAR process. Each ω_i conditional on the neighbor ω_j follows a normal distribution with mean equal to the average of neighboring districts ω_j and variance inversely proportional to the number of neighbor districtsn_i, that is; $\omega_i|\omega_j \sim N\left(\gamma \sum_{l \in \delta_i} \omega_j, \frac{\sigma_\omega^2}{n_i}\right)$, where γ quantifies the amount of spatial correlation present in the data, σ_ω^2 measures the spatial variance. ω_i and ω_j

are adjacent districts in the set of all adjacent districts δ_i of district i, and n_i are the number of adjacent districts. Following standard formulation of Bayesian regression models, we assumed vague priors; A non-informative Gaussian distributions with mean 0 and variance 10^2 for β_0, that is, $\beta_0 \sim N(0, 10^2)$. An inverse gamma prior distribution with mean 10 and variance 100 was considered for σ_ω^2, i.e. . $\sigma_\omega^{-2} \sim Ga(0.1, 0.001)$.

Similar formulations were applied for ACTs, malaria treatment seeking behavior, and household asset index, however the latter was modeled by a first stage Gaussian distribution.

A4. Bayesian variable selection

To choose the most important ITN coverage indicator that explains the maximum variation in malaria incidence, Bayesian variable selection using stochastic search was implemented separately for ITN indicators, and environmental and climatic factors. For ITN indicators, a categorical variable X_p was introduced into the model and assigned values 1 to 7 representing exclusion of the variable from the model $(I_p = 1)$, and inclusion of the six indicators as follows; proportion of existing ITNs used the previous night $(I_p = 2)$, proportion of children under five years old who slept under an ITN the previous night $(I_p = 3)$, proportion of the population that slept under an ITN the previous night $(I_p = 4)$, proportion of households with at least one ITN for every two people $(I_p = 5)$, proportion of households with at least one ITN $(I_p = 6)$, and proportion of population with access to an ITN in their household $(I_p = 7)$. Also, for lagged climatic predictors, a categorical variable Y_p was created with values 1 to 7 introduced into the model to represent exclusion of the variable from the model $(I_p = 1)$, and inclusion of different variables as follows; lag1 (continuous) $(I_p = 2)$, lag1 (categorical) $(I_p = 3)$, lag2 (continuous) $(I_p = 4)$, lag2 (categorical) $(I_p = 5)$, lag3 (continuous) $(I_p = 6)$ and lag3 (categorical) $(I_p = 7)$ For non-lagged climatic factors that is, altitude and distance to water bodies, a categorical variable Z_p

with three values was defined representing exclusion from model $(I_p = 0)$, inclusion of continuous form $(I_p = 1)$, and inclusion of categorical form $(I_p = 2)$. In the latter scenario, I_p has a probability mass function $\prod_{j=1}^{2} \pi_j^{\delta_j(I_p)}$, where π_j denotes the inclusion probabilities of functional form j (j=1,2,3) so that $\sum_{j=1}^{3} \pi_j = 1$ and $\delta_j(.)$ is the Dirac function, $\delta_j(I_p) = \begin{cases} 1, & \text{if } I_p = j \\ 0, & \text{if } I_p \neq j \end{cases}$. A spike and slab prior distribution was assumed for the regression coefficients. In particular for the coefficient β_p of the corresponding variable X_p, we assumed $\beta_p \sim \delta_1(I_p) N(0, \tau_p^2) + \left(1 - \delta_1(I_p)\right) N(0, \vartheta_0 \tau_p^2)$, that is a non-informative prior for β_p if X_p is included in the model (slab) and an informative normal prior shrinking β_p to zero (spike) if X_p is excluded from the model, setting ϑ_0 to be a large number, e.g, 10^5. Similarly, $\beta_{p,l} \sim \delta_2(I_p) N(0, \tau_{p,l}^2) + (1 - \delta_2) N(0, \vartheta_0 \tau_{p,l}^2)$ was assumed for the scenario of selecting one out of six indicators/variables or exclusion of the variable. The coefficients $\{\beta_{p,l}\}_{l=1,..,7}$ corresponding to inclusion of X_p, p=1,…,7 in the model. For inclusion probabilities, a non-informative Dirichlet distribution was adopted with hyper parameter $\alpha = (1,1,1,1,1,1,1)^T$, that is, $\boldsymbol{\pi} = (\pi_1, \pi_2, \pi_3, \pi_4, \pi_5, \pi_6, \pi_7)^T \sim \text{Dirichlet}(7, \alpha)$. We also assumed inverse Gamma priors for the precision hyper parameters τ_p^2 and $\tau_{p,l}^2$, $l = 1, \ldots, 7$.

Chapter 6: Assessing the effects of health facility readiness on severe malaria outcomes in Uganda

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Abstract

Introduction

Malaria is the leading cause of morbidity and mortality in Uganda despite the declining burden since the year 2000 when disease control was intensified. Although the effects of malaria interventions on the disease burden have been a subject of several investigations, there is a paucity of evidence for the contribution of health system performance on the disease. In this study, we assess the role of health facility readiness in Uganda on severe malaria outcomes (i.e. deaths and severe cases) among lower level facilities (HCIIIs and HCIIs).

Methods

Severe malaria outcome data was extracted from the Health Management Information System (HMIS) for the period of January - December 2013. General service and malaria-specific readiness indicators were obtained from the 2013 Uganda Service Delivery Indicator (USDI) survey. Bayesian geostatistical negative binomial models using stochastic search variable selection were fitted to the severe malaria outcomes to select the most important facility readiness indicators. Multiple Correspondence Analysis (MCA) applied on the selected indicators was used to construct a composite facility readiness scores and a categorical index based on multiple factorial axes. Geostatistical negative binomial models were employed to assess the effect of facility readiness index on the severe malaria outcomes. The analysis was carried out separately for HCIIIs (sub-county) and HCIIs (parish) facility levels.

Results

Malaria-specific readiness was achieved in only one quarter of the facilities. It was eight times higher in HCIIIs than in HCIIs and two times higher in private compared to government managed facilities. The composite readiness score explained 48% of the variation in the original indicators for HCIIIs compared to 23% explained by the first axis alone. Similar results were obtained for HCIIs (i.e. 46% versus 27%, respectively). Mortality rate was 64%

(IRR=0.36, 95%BCI: 0.14-0.61) and 68% (IRR: 0.32, 0.12-0.54) lower in the medium and high readiness groups, respectively compared to the low readiness one. Similarly, the incidence rates of severe malaria cases were lower in the medium and high readiness groups for both, HCIIIs and HCIIs.

Conclusion

A composite readiness index created by multiple factorial axes of MCA is more informative and consistent than the one based on the first axis. In Uganda, higher facility readiness is associated with a reduced risk of severe malaria outcomes in lower level facilities. However, this readiness remains low mainly due to severe absence of basic amenities and stock-out of essential medicines.

Key words: Composite facility readiness index, severe malaria outcomes**,** multiple correspondence analysis, Uganda service delivery indicator survey, Health management information system, Bayesian geostatistical models

6.1 Introduction

The global malaria burden has declined in the last decade with the incidence of cases and malaria-related deaths reducing by 18% and 48%, respectively during 2000-2015 (Bhatt et al., 2015b). Nevertheless, the disease remains a major public health problem and accounts for over 210 million cases and 420,000 deaths annually, affecting mainly the sub-Saharan Africa (World Health Organization, 2016).

In Uganda, malaria is a major leading cause of hospitalization and death, responsible for 30-50% of all health facility outpatient visits, 15-20% hospital admissions, and over 20% of hospital deaths (National Malaria Control Program, 2016). Malaria burden has also reduced in the last few years with malaria incidence declining by over 75% between 2000 and 2015 (National Malaria Control Program, 2016). Although the contribution of control interventions towards malaria decline in Uganda has been investigated (Ssempiira et al., 2017c), there is a paucity of evidence for the role health system strengthening has had on this success. This may be attributed mainly to the lack of direct measurements of health systems strengthening (WHO, 2001), and partly to the weak routine data collection systems in developing countries (Yeka et al., 2012). The rollout of the District Health Information System version 2 (DHIS2) in Uganda has facilitated electronic reporting of routinely collected health facility data and has led to improvements in data quality (Kiberu et al., 2014).

Health system strengthening can be measured indirectly using proxies of its six building blocks, that is, governance, health workforce, health financing, health technologies, health information and service delivery (The malERA Consultative Group on Health Systems and Operational, 2011). Service delivery is primarily concerned with immediate outputs of a national health system (Backman et al., 2008). The proxy measure for service delivery is health facility readiness defined in terms of general service and service-specific readiness indicators (WHO, 2001) estimated from health facility surveys.

General service readiness refers to the overall capacity of health facilities to provide health services and is measured by the availability of tracer items in five domains, namely; basic amenities, basic equipment, standard precautions for infection prevention, diagnostic capacity and essential medicines (World Health Organization, 2015b). Service-specific readiness, on the other hand, refers to the capability of health facilities to provide a service of minimum acceptable standards, and is measured by the availability of the following tracer items necessary for the provision of a particular service; trained staff, service delivery guidelines, equipment, diagnostic capacity, medicines and commodities (World Health Organization, 2015b).

Although measurements of facility readiness is crucial for health planning and decision making, the implementation of nationally representative facility surveys in Uganda has suffered from lack of funds. The most recent survey namely, the Uganda Service Delivery Indicator (USDI) was conducted in 2013 and it was supported by the World Bank (Wane and Martin, 2013). USDI provides a set of metrics for benchmarking service delivery performance in health and education and assesses the quality of basic health services and of services related to primary education. It adopted health facility assessment tools used in service provision assessments designed by the World Health Organization (WHO) (World Health Organization, 2010). A high number of health facility readiness indicators, corresponding to tracer items can be generated from these surveys, each measuring a different attribute of readiness but no single indicator is sufficient to summarize all aspects of facility readiness. Therefore, a need arises to develop a single index of readiness that represents the vast array of readiness indicators characterizing health system functioning and its effect on health outcomes.

Facility readiness indices have been developed in assessment surveys conducted in several countries including Nigeria (Gage et al., 2016a; Oyekale, 2017), Ghana (Boyer et al., 2015), Haiti (Wang et al., 2010), Tanzania (Jackson et al., 2015), Brazil (Gouws et al., 2005),

Malawi and Nepal (Leslie et al., 2017), Kenya, Namibia and Rwanda (Kruk et al., 2016) to assess the effects of health facility readiness on health outcomes. In most of these studies, the index was developed using Principal Component Analysis (PCA) designed for summarizing continuous variables (Howe et al., 2012), despite the fact that the data collected from the facility assessments surveys are mainly binary in nature. Multiple correspondence analysis (MCA) is the most appropriate technique for this type of categorical data (Amek et al., 2015; Boyer et al., 2015; Traissac and Martin-Prevel, 2012). A few studies that have employed MCA to construct a facility readiness index using the first factorial axis to represent overall facility readiness (Ayele et al., 2014; Kollek and Cwinn, 2011). However, the use of this single-axis index is unlikely to fulfill the Global First Axis Ordering Consistency (FAOC-G) property (Asselin, 2009) which means that the score monotonically increases/decreases for all indicators. The FAOC-G property ensures that the absence of any readiness indicator from a facility will contribute to a lower readiness score than its presence. Failure of the FAOC-G will result to inconsistent and meaningless readiness score. Asselin (2009) (Asselin, 2009) proposed a composite index based on more than one MCA axis to remedy the construction of inconsistent poverty scores. To our knowledge, composite MCA scores have not been used in constructing indices measuring health systems performance.

In this study, we linked USDI survey data of 2013 with severe malaria outcomes data reported in the Health Management Information System (HMIS) to assess the effects of facility readiness on severe malaria outcomes. A composite readiness score was created by exploiting more than one factorial axis of the MCA of the most relevant general service and malaria specific readiness indicators identified through geostatistical variable selection. Results from this study will inform the Ministry of Health (MoH) and other stakeholders on the overall readiness of lower level health facilities in Uganda to deliver malaria services, and the role of this effect on the risk of severe malaria outcomes.

6.2 Methods

6.2.1 Settings

Uganda is located in the SSA region and ranks among the top 15 countries that contribute to 90% of the global malaria burden. Malaria transmission is stable and perennial in 95% of the country, but the entire population is at risk (Uganda Bureau of Statistics, 2016). The remaining 5% of the country comprises of unstable and epidemic-prone transmission areas situated in highlands of the south-western, and areas around the mountains Rwenzori in the mid-western region and Elgon in mid-eastern. *Plasmodium falciparum* is the dominant parasite species and the most dangerous with the highest case-fatality rate. The primary vector is *Anopheles gambiae s.l.* which breeds in temporary stagnant water, while An. *funestus* is the second most important vector and breeds mainly in permanent water bodies.

6.2.2 National health system

The health system in Uganda is decentralized with the Ministry of Health responsible for policy formulation, quality assurance, resource mobilization, capacity development, technical support, and provision of nationally coordinated services such as epidemic control, coordination of health research and monitoring and evaluation of overall sector performance. Health care services are delivered through a tiered structure of facilities consisting of hospitals and Health Centers (HC) IV, HCIII, HCII and HCI at district, Health Sub-District (HSD), sub-county, parish and village levels, respectively (Uganda Ministry of Health, 2014). Hospitals are further classified into district, regional referral, national referral serving district, region and country-level populations. HCIVs, HCIIIs, and HCIIs serve populations at the county, sub-county and parish level, respectively. The HCI is the lowest level and first point of contact. It is headed by village health teams (VHT)/community medicine distributors who are largely volunteers, targeting smaller populations of 1000 people.

6.2.3 Data sources

6.2.3.1 Severe malaria outcomes

Data on severe malaria outcomes was extracted from the Health Management Information System (HMIS) for the period January – December 2013. Two severe malaria outcomes were defined, namely, the cumulative number i) of malaria deaths and ii) of severe malaria cases leading to hospitalization during 2013. Both outcomes were considered for the analyses of HCIII data, but only the latter for HCIIs due to the limited scope as diagnosed severe cases are referred to HCIIIs and other higher level facilities.

6.2.3.2 Statistical methods

Data from the USDI survey were used to construct readiness indicators following standard definitions (World Health Organization, 2015b). In particular, we created i) general service readiness indicators for the five domains (i.e. basic amenities, basic equipment; standard precautions for infection prevention; diagnostic capacity and essential medicines) and ii) malaria-specific indicators. Readiness indicators were defined as binary variables, taking the value '1' if the tracer item was available at the facility and '0' otherwise. Availability and functionality of items were confirmed through direct observation by the interviewer prior to data recording in the questionnaire. Furthermore, domain readiness indicators for each of the five domains of the general service readiness and for the domain of malaria services were defined as availability of all tracer items that belong to a particular domain. A facility was assigned 1 if all tracer items constituting a domain were found at the facility and 0 otherwise.

Bayesian geostatistical negative binomial models using stochastic search variable selection were fitted to the severe malaria outcomes to select the most important facility readiness indicators. For each readiness indicator, a Bernoulli variable was introduced with Bernoulli probability corresponding to the inclusion of the indicator in the model (details are provided in the Appendix). Spatial correlation was taken into account by assuming a Gaussian process on health facility locational random effects. The models were fitted separately on

severe malaria and malaria mortality for HCIII facilities and on severe malaria for HCII facilities.

MCA was applied to most important K readiness indicators selected with posterior inclusion probabilities of at least 50% to construct a facility readiness score. For each indicator, two binary variables were created corresponding to the presence and absence of the indicator/tracer from the facility. A readiness score, $F_i^a = \frac{1}{K}\sum_{k=1}^{K}\sum_{j_k=0}^{1} W_{j_k}^{a,k} I_{j_k,i}^{k}$, where $I_{j_k,i}^{k}$ is a binary variable 0/1 taking the value 1 when facility i has the category j_k for the indicator k and the weights $W_{j_k}^{a,k}$ are the corresponding column standard coordinates on the a^{th} factorial axis. Typically, a score is defined on the first factorial axis, i.e., $a = 1$. Following the approach proposed by Asselin (2009) we defined the composite readiness score F_i by $F_i = \frac{1}{K}\sum_{k=1}^{K}\sum_{j_k\in\{0,1\}}\sum_{a=1}^{L}\delta(k-a)W_{j_k}^{a,k}I_{j_k,i}^{k}$, where L is the number of factorial axes used in the composite score and $\delta(k-a)$ is the Dirac delta function which takes the value 1 when the k^{th} indicator is defined on the a^{th} factorial axis and 0 otherwise, that is, $\delta(k-a) = 1$ if $k = a$ and $\delta(k-a) = 0$ if $k \neq a$. Identification of the factorial axis that will represent the k indicator depends on a discrimination measure calculated for each indicator and axis, measuring the contribution of the indicator to the total variance explained by the axis. To improve interpretation of the score we translate the weights so that the absence category $(j_k = 0)$ of the k indicator to receive a zero weight and the presence one $(j_k = 1)$ to receive a strictly positive one representing the gain in the readiness increase measured by the axis a when a facility i acquires the k tracer. Therefore, the $W_{j_k}^{a,k}$ in F_i is replaced by $W_{j_k}^{+a,k}$ where $W_0^{+a,k}$=0 and $W_1^{+a,k} = W_1^{a,k} - W_0^{a,k}$. Details on this procedure are provided in the Appendix.

A separate composite score was derived for each health facility level due to differences in mandate and service scope across levels. A readiness index was created from the readiness score as a categorical variable with three levels for both HCIIIs and HCIIs based on the distribution of the composite score.

Descriptive statistics, that is, frequencies, proportions and chi-square tests were used to summarize and compare readiness indicators and scores by facility level and other health facility characteristics. Geostatistical Bayesian negative binomial models were fitted separately by facility level to assess the effect of health facility readiness on the severe malaria outcomes. The models were adjusted for facility location (rural/urban), management authority (Government/private) and distance to district headquarters.

Descriptive analysis and MCA were conducted in STATA (Stata Technical Support, 2015) and Bayesian models were fitted in OpenBUGS (Lunn et al., 2000) using Markov Chain Monte Carlo (MCMC) simulation. Parameters were summarized by their posterior medians and 95% Bayesian Credible intervals (BCIs). Modeling details are provided in the Appendix.

6.3 Results

6.3.1 Health facility characteristics

A total of 250 health facilities participated in the health facility assessment survey but only 207 (82.8%) reported in the HMIS consistent and complete data on severe malaria outcomes during January-December 2013. Six out of the 207 were higher level facilities (i.e. hospitals and HCIVs) and were excluded due to insufficient sample size. The characteristics of the 201 facilities included in the analysis are presented in Table 6.1. Most facilities were HCIIIs, government-managed, rural-based, and were located more than 10km from district headquarters. The average travel time from the district headquarters to a facility using public means of transport was an hour. HCIIIs offered outpatient consultations on average seven days a week, 15 hours a day. HCIIs operated six days a week, 12 hours per day. A total of 87,719 severe malaria outcomes were reported from the 201 facilities during the study period, 86,848 (99%), of which were severe malaria cases and 871 were malaria-related deaths. The majority (61,642) of outcomes were reported by HCIIIs. The number of severe malaria cases and malaria-related deaths was twice as high in children less than 5 years than in older

individuals. The distribution of severe malaria outcomes is shown in Figure 6.1 and suggests a higher burden in areas of the north and western parts of the country compared to the central areas.

Table 6.1: Health facility characteristics

Characteristic	Total (N=201) n (%)	HCIIIs (N=105) n (%)	HCIIs (N=96) n (%)
Managing authority			
Government	146 (72.6)	76 (72.4)	71 (74.0)
Non-government	55 (27.4)	29 (27.6)	25 (26.0)
Location type			
Rural	166 (82.6)	83 (79.1)	83 (86.5)
Urban	35 (17.4)	22 (21.0)	13 (13.5)
Distance to district headquarters			
0-10 km	52 (25.9)	28 (26.7)	24 (25.0)
>10 km	149 (74.1)	77 (73.3)	72 (75.0)
Region			
Central	47 (23.4)	23 (21.9)	24 (25.0)
Eastern	51 (25.4)	29 (27.6)	22 (22.9)
Kampala	10 (5.0)	5 (4.8)	5 (5.2)
Northern	33 (16.4)	22 (21.0)	11 (11.5)
Western	60 (29.9)	26 (24.8)	34 (35.4)
	Mean (sd)	**Mean (sd)**	**Mean (sd)**
Days per week facility is open	6.4 (1.0)	6.7 (0.9)	6.0 (1.1)
Hours per day facility is open	12.9 (6.4)	14.1 (6.9)	11.6 (5.5)
Travel time from facility to district headquarters (hours)	1.1 (1.1)	1.0 (1.1)	1.2 (0.9)
Proportion of malaria deaths*	%	%	%
All ages	0.98	1.14	0.61
< 5 years	1.09	1.13	0.96
>=5 years	0.85	1.16	0.31

*of the total severe malaria outcomes

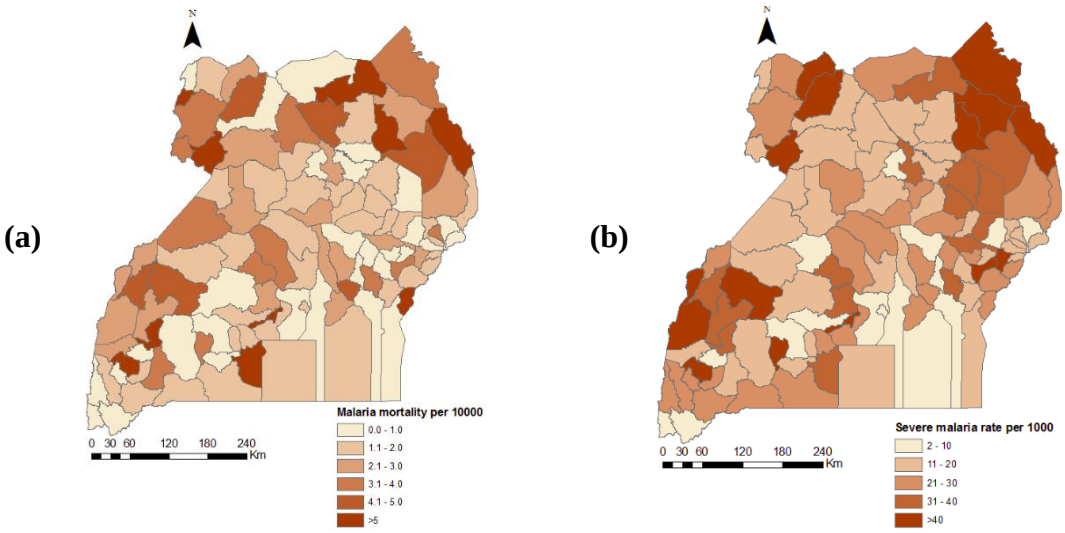

Figure 6.1: Geographical distribution of severe malaria outcomes in Uganda in 2013; (a) mortality, (b) severe cases

General service and malaria specific readiness indicators

General service and malaria specific readiness indicators for HCIIIs and HCIIs are presented in Table 6.2 by domain along with their posterior inclusion probabilities.

Results show that basic amenities readiness was achieved in only three HCIII facilities and none in HCII. Access to adequate sanitation and availability of emergency transport were the most and least available tracer items in this domain. Urban-based facilities had a significantly higher basic amenities readiness compared to rural facilities (p-value=0.023) (Table A6.1, Appendix).

Fifty percent of facilities (irrespective of level, HCIII and HCII) achieved basic equipment readiness. This readiness was significantly higher in HCIIIs, urban-located, private managed and in Central region facilities but did not differ by the proximity of a facility to district headquarters (Table A6.1, Appendix).

Standard precautions readiness was attained in close to five percent of the facilities, despite of high availability of most of the single tracer items. The commonest standard

precaution items found at facilities were disposable syringes and needles, sharps container box, and disposable gloves, while the least available item was incinerator for final disposal of sharps. Standard precautions readiness was significantly higher among private managed (P-value=0.007) and urban facilities (p-value=0.002).

Diagnostic capacity readiness was met in only one-fifth of facilities. This readiness was more than five times higher in HCIIIs compared to HCIIs, two times more in urban than rural facilities. Diagnostics readiness was higher in private-managed facilities and highest in the Northern region but did not differ by the distance to district headquarters (Table A1, Appendix). The majority of the facilities had malaria RDTs but very few had urine dipstick used in measuring glucose levels. An average of three diagnostic tests were available in HCIIIs but only one in HCIIs.

Facility readiness for essential medicines was achieved in less than five percent in HCIII and in none of HCII facilities. On average, only three out of nine medicines assessed were available at both types of facilities. Availability of individual essential medicines was significantly higher in HCIIIs. Oral rehydration solution and zinc sulphate tablets were among the most available medicines, whereas magnesium sulphate and oxytocin injections were the least available. Private facilities, situated in urban places and close to the district headquarters had a significantly higher readiness for essential medicines.

Table 6.2: General service, malaria specific readiness indicators and posterior inclusion probabilities

Readiness indicator	HCIIIs N=105			HCIIs N=96	
	Readiness n (%)	Inclusion probability		Readiness n (%)	Inclusion probability
General service		Severe malaria cases (%)	Malaria deaths (%)		Severe malaria cases (%)
Basic amenities†	**3 (2.9)**			**0 (0.0)**	
Uninterrupted power supply	45 (42.9)	47.0	37.3	32 (33.3)	34.1
Improved water source inside or within source of facility	37 (35.2)	68.0*	67.8*	21 (21.9)	44.0
Access to adequate sanitation facilities for clients	94 (89.5)	42.0	44.3	88 (91.7)	43.6
Communication equipment (phone or short wave radio)	22 (21.0)	41.3	43.4	6 (6.3)	43.0
Access to computer with email/internet access	21 (20.0)	38.7	37.9	8 (8.3)	43.0
Emergency transportation	16 (15.2)	34.4	39.8	5 (5.2)	60.8*
Basic equipment†	**63 (60.0)**			**38 (39.6)**	
Adult scale	87 (82.9)	61.1*	59.2*	70 (72.9)	34.4
Child scale	89 (84.8)	38.8	39.2	70 (72.9)	60.6*
Thermometer	88 (83.8)	42.4	42.6	75 (78.1)	56.5*
Stethoscope	98 (93.3)	39.7	44.1	80 (83.3)	32.4
Blood pressure apparatus	91 (86.7)	42.6	39.4	77 (80.2)	33.2
Standard precautions for infection prevention†	**5 (4.8)**			**4 (4.2)**	
Sterilization equipment	29 (27.6)	36.3	39.3	7 (7.3)	40.4
Appropriate storage of sharps waste	101 (96.2)	40.9	42.2	93 (96.9)	75.7*
Safe final disposal of sharps	15 (14.3)	39.1	40.9	10 (10.4)	42.6
Disposable syringes with disposable Needles	101 (96.2)	46.9	40.5	93 (96.9)	50.7*
Disposable gloves	98 (93.3)	55.6*	64.0*	94 (97.9)	51.6*
Diagnostic capacity†	**34 (32.4)**			**6 (6.3)**	
Malaria RDTs	83 (79.1)	70.5*	72.8*	72 (75.0)	38.0
Blood glucose	52 (49.5)	39.2	27.2	12 (12.5)	57.0*
HIV diagnostic capacity	89 (84.8)	47.7	51.0*	37 (38.5)	30.3
Urine dipstick	74 (70.5)	25.8	39.5	14 (14.6)	40.0
Essential medicines†	**5 (4.8)**			**0 (0.0)**	
Amoxicillin syrup/suspension or dispersible tablet	24 (22.9)	45.0	50.7*	17 (17.7)	61.0*
Ampicillin powder for injection	72 (68.6)	50.5*	53.2*	7 (7.3)	45.1
Ceftriaxone injection	41 (39.1)	63.5*	56.0*	60 (62.5)	32.5
Gentamicin injection	52 (49.5)	52.2*	56.2*	21 (21.9)	38.2
Magnesium sulphate injectable	58 (55.2)	55.9*	58.6*	5 (5.2)	46.4
Oral rehydration solution	87 (82.9)	31.9	39.2	74 (77.1)	38.0
Oxytocin injection	58 (55.2)	57.3*	53.3*	5 (5.2)	41.4
Zinc sulphate tablets, dispersible tablets or syrup	77 (73.3)	62.9*	54.7*	64 (66.7)	41.4
Malaria service†	**45 (42.9)**			**8 (8.3)**	
Microscopy	81(77.1)	63.8*	65.5*	16 (16.7)	74.2*
Artemisinin Combination Therapies (ACTs)	88 (83.8)	38.4	38.0	86 (89.6)	39.3
Fancidar	94 (89.5)	34.6	43.8	77 (80.2	28.6
Artesunate	5 (4.8)	45.4	41.7	2 (2.1)	63.9*

†*Domain readiness indicators are defined as availability of all tracer items belonging to the domain*
**Posterior probability of inclusion >50%*

Malaria-specific readiness was achieved in only one quarter of the facilities. It was eight times higher in HCIIIs and two times more in private managed compared to HCIIs and government managed facilities, respectively. However, readiness did not differ by location, region, and distance from district headquarters (Table A6.1, Appendix). In spite of the overall low malaria readiness, the proportion of facilities with RDTs and ACTs was high but varied with regions.

Geostatistical variable selection results showed that the same indicators were equally important for explaining variation in severe malaria cases and malaria-related deaths for HCIII facilities. More so, for HCIIIs, the essential medicines domain and for HCIIs the standard precautions for the infection prevention domain had the highest number of indicators related to malaria outcomes. Availability of RDTs, and appropriate storage of sharps waste were statistically important for HCIIIs and HCIIs, respectively. The disposable gloves were the only indicator selected in both HCIIIs and HCIIs types of facilities.

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6.3.3 Facility readiness score and index

MCA was applied on the readiness indicators selected from the variable selection procedure to obtain a readiness score. Since the stochastic variable selection model identified the same set of indicators in HCIIIs as being important for both severe malaria outcomes, a single readiness score was created at this level.

Tables 6.3 and 6.4 display the standard coordinates of readiness indicators obtained from the first seven and five factorial axes for HCIIIs and HCIIs, respectively. Results show that for HCIIIs on the first factorial axis, a subset of five indicators met the FAOC-G requirement in the positive direction, while a second subset of six indicators met this requirement in the negative direction. Therefore, there are two subsets of indicators that are inconsistent and one subset should have been discarded, leading to a loss of information if we had constructed the score using the first factorial axis. For HCIIs, all but one indicator met the FAOC-G requirement. However, four of the selected indicators possess higher discrimination power on axes other than the first one.

The composite facility readiness score explained 47.6% of the total variation in the indicators from HCIIIs compared to 23% explained by the score based on the first factorial axes (Figure A6.1, Appendix). Similarly, for HCIIs, the variation explained by the composite score was 45.8% which is almost two times higher than that explained by the first axis, i.e., 26.6%. Furthermore, our approach of including in the score construction the indicators identified by the variable selection gave a more informative score than the score we would have constructed from all indicators. In particular, the latter for HCIII explained 27.9% (composite) and 12.2% (first factorial axis) of the total variation. For HCII, these figures were 26.8% and 16.6%, respectively. Therefore, we relied the analysis on the composite score based on the subset of selected indicators.

The indicators with the highest weights in the composite score (Tables A6.2 and A6.3 in the Appendix) are availability of disposable gloves and malaria Rapid Diagnostic Test (RDTs) kits (for HCIIIs), availability of disposable gloves, single use auto-disable syringes, and appropriate storage of sharps waste (for HCIIs). The composite scores show a nearly normal distribution and a weakly normal distribution with long tails for HCIIIs and HCIIs, respectively (Figure A6.2, Appendix). The regional average facility readiness score was

higher in the central and southern located regions and lower in the eastern and northern areas of the country for both HCIIIs and HCIIs (Figure 6.2).

Table 6.3: Standard coordinates of readiness indicators on the first seven factorial axes (HCIIIs)

Indicator	Category	Frequency distribution	Factorial axes[a]						
			1	2	3	4	5	6	7
Improved water source	Yes	37 (35.2)	0.77 [b]	1.32	0.91	1.52	0.16	**3.18**	1.96
	No	68 (64.8)	-0.42	-0.72	-0.50	-0.83	-0.09	**-1.73**	-1.06
Adult scale	Yes	87 (82.9)	0.05	**-0.80**	0.50	-0.34	-0.07	0.19	0.39
	No	18 (17.1)	-0.26	**3.86**	-2.42	1.64	0.37	-0.94	-1.90
Disposable gloves	Yes	98 (93.3)	0.12	0.05	-0.24	**-0.60**	0.16	0.40	-0.29
	No	7 (6.7)	-1.69	-0.67	3.32	**8.33**	-2.18	-5.61	4.08
Malaria diagnostic capacity	Yes	83 (79.1)	-0.23	0.11	-0.66	0.06	**-1.23**	0.15	0.18
	No	22 (20.9)	0.86	-0.40	2.50	-0.23	**4.66**	-0.56	-0.69
Ampicillin powder for injection	Yes	72 (68.6)	**-0.83**	-0.25	-0.82	0.06	-0.31	-0.11	0.52
	No	33 (31.4)	**1.80**	0.55	1.79	-0.13	0.68	0.23	-1.15
Ceftriaxone injection	Yes	41 (39.1)	0.07	**-1.99**	-0.93	1.56	1.74	-0.26	0.11
	No	64 (60.9)	-0.04	**1.28**	0.62	-1.00	-1.12	0.16	-0.07
Gentamicin injection	Yes	52 (49.5)	0.23	**-1.94**	0.43	-0.53	-1.04	0.70	0.28
	No	53 (50.5)	-0.23	**1.90**	-0.42	0.52	1.02	-0.69	-0.27
Magnesium sulphate injectable	Yes	58 (55.2)	**-1.69**	0.18	0.99	-0.23	0.100	0.19	-0.21
	No	47 (44.8)	**2.09**	-0.22	-1.22	0.28	-0.12	-0.23	0.26
Oxytocin injection	Yes	58 (55.2)	**-1.69**	0.18	0.99	-0.23	0.10	0.19	-0.21
	No	47 (44.8)	**2.09**	-0.22	-1.22	0.28	-0.12	-0.23	0.26
Zinc sulphate tablets	Yes	77 (73.3)	-0.55	0.08	-0.75	-0.54	0.76	0.07	**1.14**
	No	28 (26.7)	1.50	-0.22	2.05	1.49	-2.09	-0.19	**-3.14**
Microscopy	Yes	81(77.1)	**-0.50**	-0.36	-0.46	0.66	0.13	0.83	-0.85
	No	24 (22.9)	**1.69**	1.21	1.57	-2.21	-0.43	-2.80	2.88
Variation explained by selected factorial scores			23.0%	14.0%	11.3%	10.2%	9.9%	7.9%	7.6%

High-lighted in bold are weights of indicators from the factorial axis selected to contribute to the composite score

[a] Results are limited to the first seven axes as there was no additional information gain beyond axis # 7

[b]Group of indicators meeting the FAOC-G in positive direction (shaded grey) and those meeting FAOC-G in negative direction (not shaded)

Table 4: Standard coordinates of readiness indicators on the first five factorial axes (HCIIs)

Indicator	Category	Frequency distribution	Factorial axes[a]				
			1	2	3	4	5
Emergency transportation	Yes	5 (5.2)	**6.43**[b]	0.07	2.01	0.36	2.33
	No	91 (94.8)	**-0.35**	-0.004	-0.11	-0.02	-0.13
Child scale	Yes	70 (72.9)	0.25	**1.08**	0.42	-0.28	1.14
	No	26 (27.1)	-0.67	**-2.89**	-1.09	0.75	-3.06
Appropriate storage of sharps waste	Yes	93 (96.9)	0.04	0.26	0.187	-0.26	**-0.34**
	No	3 (3.1)	-1.07	-7.90	-5.81	8.18	**10.61**
Single use standard disposable or auto-disable syringes	Yes	93 (96.9)	0.06	0.05	**-0.38**	-0.19	0.15
	No	3 (3.1)	-1.77	-1.58	**11.78**	5.98	-4.77
Disposable gloves	Yes	94 (97.9)	-0.01	-0.22	0.09	**-0.34**	0.10
	No	2 (2.1)	0.44	10.16	-4.41	**15.79**	-4.65
Glucometer	Yes	12 (12.5)	**4.11**	1.09	0.21	1.97	0.01
	No	84 (87.5)	**-0.59**	-0.16	-0.03	-0.28	-0.001
Amoxicillin syrup, suspension or dispersible tablet	Yes	17 (17.7)	**2.40**	-2.60	-0.97	0.18	-1.60
	No	79 (82.3)	**-0.51**	0.56	0.21	-0.04	0.34
Thermometer	Yes	75 (78.1)	0.31	0.439	**-0.90**	-0.33	-0.48
	No	21 (21.9)	-1.10	-1.57	**3.23**	1.18	1.73
Microscopy	Yes	16 (16.7)	**3.21**	-0.88	0.79	-0.93	0.03
	No	80 (83.3)	**-0.64**	0.18	-0.16	0.19	-0.01
Artesunate	Yes	2 (2.1)	**8.07**	-2.49	2.32	1.44	-0.68
	No	94 (97.9)	**-0.17**	0.05	-0.05	-0.03	0.01
Variation explained by selected factorial axes			24.9%	4.1%	8.6%	5.3%	3.1%

High-lighted in bold are weights of indicators from the factorial axis selected to contribute to the composite score

[a] Results are limited to the first five axes as there was no additional information gain beyond axis # 5

[b]Group of indicators meeting the FAOC-G in positive direction (shaded grey) and those meeting FAOC-G in negative direction (not shaded)

We used the tertiles for the score distributions to create a categorical readiness index with three categories for HCIIIs and HCIIs. The levels of the index were treated as order proxies for the low, medium and high readiness levels for the first, second and third levels, respectively.

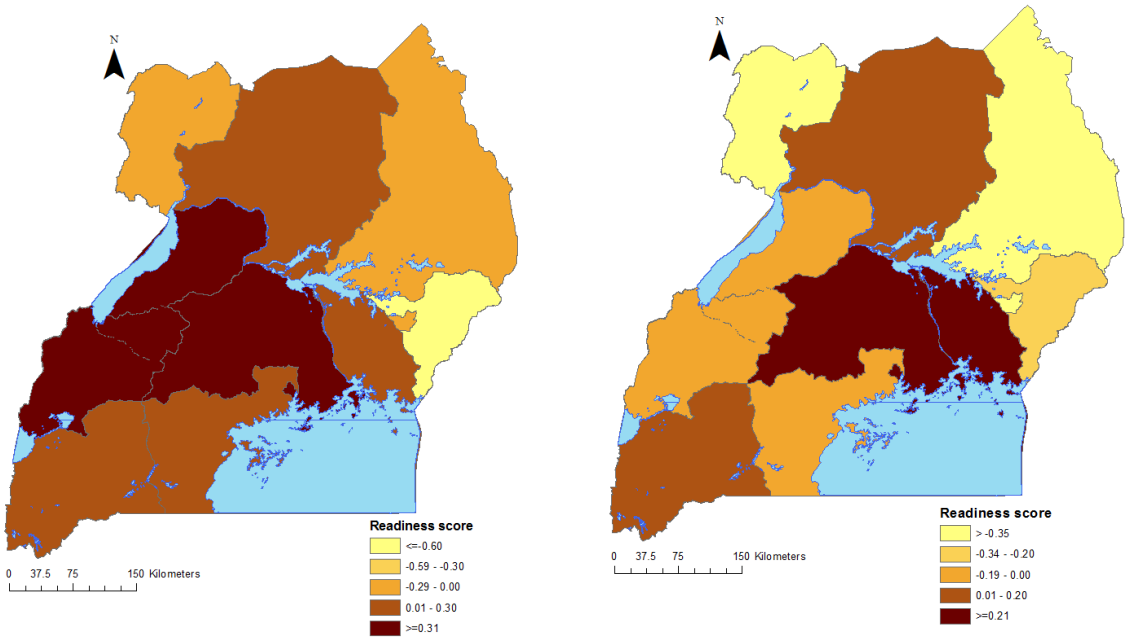

Figure 6.2: Regional distribution of facility readiness score; (a) HCIIIs, (b) HCIIs

6.3.4 Effects of facility readiness on severe malaria outcomes

Estimates of the effect of the composite facility readiness index on the malaria outcomes based on the selected indicators are presented in Table 6.5. For HCIIIs, malaria-related mortality decreased with increasing readiness index. Mortality rate was 64% (IRR=0.36, 95%BCI: 0.14-0.61) and 68% (IRR=0.32, 95%BCI: 0.12-0.54) lower in the medium and high compared to low readiness groups, respectively. Malaria mortality was statistically lower in facilities located in urban areas, but did not differ by ownership, and distance to district headquarters. The incidence rate of severe malaria cases was 19% (IRR=0.81, 0.56-0.93) and 76% (IRR=0.24, 0.16-0.38) lower in the medium and high readiness groups, respectively compared to the low group. Severe malaria cases differed by facility location, but there was no relationship observed for the distance to district headquarters, and ownership type (i.e. private vs government).

For HCIIs, the incidence rate of severe malaria cases was 44% (IRR=0.56, 0.26-0.91) and 30% (IRR=0.70, 0.42-0.94) lower in the medium and high groups, respectively compared to the low one. The incidence of severe cases was twice as high among distant HCIIs

compared to those near to the district headquarters. However, the distance effect was not important for HCIIIs. Geographical variation in severe malaria cases was higher in HCIIs than in HCIIIs.

We repeated the analysis of the relation between facility readiness and severe malaria outcomes using a composite readiness score constructed from all indicators to assess the impact of our approach on the estimated facility readiness effects. Results showed that the composite score constructed from all indicators suggested that the relation between readiness with severe malaria (for HCIIs) and with malaria deaths (for HCIIIs) were not statistically important (Table A6.4 in the Appendix).

Table 6.5: Posterior estimates (median and 95% BCI) of the effects of composite facility readiness index on severe malaria outcomes estimated from Bayesian geostatistical negative binomial models

Characteristic	HCIIIs		HCIIs
	Malaria deaths	Severe malaria cases	Severe malaria cases
	IRR (95%BCI)[1]	IRR (95%BCI)	IRR (95%BCI)
Readiness index			
Low	1	1	1
Medium	0.36 (0.14, 0.61)*	0.81 (0.56, 0.93)*	0.56 (0.26, 0.91)*
High	0.32 (0.12, 0.54)*	0.24 (0.16, 0.38)*	0.70 (0.42, 0.94)*
Location			
Rural	1	1	1
Urban	0.58 (0.20, 0.86)*	0.74 (0.63, 0.85)*	3.42 (0.92, 5.26)
Ownership			
Government	1	1	1
Private	0.76 (0.48, 1.90)	4.60 (0.90, 7.46)	1.34 (0.82, 3.04)
Distance to district headquarters			
<=10km	1	1	1
>10km	0.76 (0.48, 0.92)	0.45 (0.36, 0.75)	2.27 (1.34, 4.04)*
Spatial parameters			
Spatial variance	1.45 (1.10, 1.82)	0.61 (0.49, 0.99)	0.58 (0.36, 0.71)
Range (km)	5.47 (2.77, 16.64)	4.26 (2.73, 13.21)	35.51 (4.65, 70.31)

**statistically important effect; [1]IRR: Incidence Rate Ratio*

6.4 Discussion

We constructed a composite facility readiness index for HCIIIs and HCIIs using the Uganda service delivery indicators survey data of 2013 and used it to assess the effects of health facility readiness on severe malaria cases and malaria-related deaths in the country during January-December 2013. We used multiple correspondence analysis based on the most relevant general service and malaria service readiness indicators for severe malaria outcomes identified through geostatistical variable selection.

Our findings suggest that the composite readiness score constructed from more than the first axis contains more information as it explains a higher proportion of the variation in the original data for both HCIIIs and HCIIs unlike the index constructed from the first axis. Our findings are in agreement with results reported in economics literature in which the concept of composite score was first developed to evaluate poverty reduction programmes (Alkire and Foster, 2011; Kakwani and Silber, 2008; Lemmi and Betti, 2006). However, the inclusion of multiple factorial axes in the score construction has not been applied yet in the epidemiological studies of health system performance (Amek et al., 2015; Boyer et al., 2015; Traissac and Martin-Prevel, 2012). These studies rather use the first MCA axis without any regard to whether the Global Facility Axis Ordering Consistency (FAOC-G) property is met. This leads to indices that explain a small proportion of variation in the original data thus resulting in a weak and less representative index that is not capable of describing all facets of readiness in the population of interest. The composite index has been shown to demonstrate that overall readiness is a multidimensional concept that cannot be captured using only one axis but by integrating all the different aspects of readiness present in other axes to arrive at a robust index (Alkire and Foster, 2011).

More so, the index based on the subset of indicators identified through variable selection contained more information and had an important effect on the risk of severe outcomes compared to the index created from all indicators. The probable explanation to this

finding is that variable selection helps to weed out indicators from the index construction that have little or negligible relationship with the outcome of interest and hence resulting in a meaningful index. This is the first readiness index study where such an objective procedure has been applied to select the most important indicators to create an index.

Our results also suggested that facility readiness is unevenly distributed across regions with the northern regions having the least readiness compared to the central and sourthen located regions. These regional differences between the north and south can be explained by the by the blow that the recent war had on the health infrastructure which has severely affected the availability and access to health services in this region (Ssempiira et al., 2017d, 2017c).

Indicators that contributed the most weight to the composite index were those with a high coverage, indicating that their domination of the original data was carried over to the reduced dimension space of the index. These results are in agreement with findings from other studies (Boyer et al., 2015; Filmer and Pritchett, 2001; Jackson et al., 2015; McKenzie, 2005; Vyas and Kumaranayake, 2006).

Furthermore, the readiness indicators that explained most variation in severe malaria outcomes differed between HCIIIs and HCIIs. This could be attributed to the different mandates of facilities at different levels owing to variations in service scope, staffing levels, infrastructure and equipment (Ministry of Health (MOH) [Uganda] and Macro International Inc., 2008).

The readiness score had a nearly normal distribution for HCIIIs and a long-tailed thin normal distribution for HCIIs. This is an indication of higher heterogeneity in readiness of HCIIs compared to HCIIIs and can be explained by the HCIIs' limited capacity to provide quality basic healthcare services as a result of low staffing levels, high drug stock-outs, insufficient infrastructure, and poor coordination and limited supervision unlike in HCIIIs and

higher level facilities (Ministry of Health (MOH) [Uganda] and Macro International Inc., 2008).

Our study results that readiness of lower facilities to provide malaria services was low despite the high availability of the domain-specific tracer items. Absence of microscopy diagnostic testing is the main reason for this shortcoming. The inadequate malaria readiness at the lower level facilities which serve a big proportion of the rural population may explain why the disease remains the leading cause of mortality in the country (Uganda Ministry of Health, 2014).

However, generally malaria-specific readiness was higher in HCIIIs, urban-located privately-managed facilities, and in facilities located nearer district headquarters. This is because HCIIIs receive more Primary Health Care (PHC) funding, have better infrastructure, more qualified personnel and are subject to more supervision from both technical and political teams at district and health sub-district level compared to HCIIs (Uganda Ministry of Health, 2014).

The higher malaria readiness in privately managed facilities may be attributed to better medical equipment, well-maintained infrastructure, higher staffing levels, reduced staff absenteeism and higher supervision compared government-managed facilities (Oketcho et al., 2015). Urban facilities have also higher malaria readiness most likely due to greater access to infrastructure including road network, national power grid and other public services, which eases transportation and delivery of commodities such as drugs, supervision, and improves staff morale which boosts retention.

Facility readiness was very low for all general service domains with the exception of that basic equipment. This can be attributed to inadequate government health sector funding which stands at 9.6% of the national budget and it is way below the Abuja Declaration target of 15% (Agaba, 2009). The low sector funding affects negatively the maintenance of

infrastructure, causes stock-outs of essential drugs, slows down recruitment and motivation of the health workforce (Uganda Ministry of Health, 2014).

The high readiness in the basic equipment domain could be explained by the durable nature and low cost of the tracer items that constitute this domain compared to other domains whose items may cost higher and require substantial massive capital investment or they are consumables such as drugs that require constant replenishment.

Diagnostic capacity readiness was very low, despite the high availability of malaria RDTs in the facilities. This can be attributed to the country's adoption of the WHO 'Test and Treat' campaign where free RDTs are provided by the ministry of health with support from Roll Back Malaria (RBM) partnership to public and private facilities (Uganda Bureau of Statistics and ICF International, 2015). The high availability of RDTs in the lower-level facilities is an indication that the majority of malaria cases reported in the HMIS are confirmed. Availability of glucometers for measuring blood glucose was low especially at HCIIs indicating a major setback in lieu of emerging evidence of a growing non-communicable diseases burden in Uganda (Schwartz et al., 2014).

More so, essential medicines readiness was low despite some medicines such as oral rehydration solution and zinc sulphate drugs were highly available. This finding is consistent with MoH reports that highlight drug stock-outs as one of the major constraints to good service delivery in Uganda (Uganda Ministry of Health, 2015).

Results further indicated that the readiness of both HCIIIs and HCIIs was associated with a decline in malaria-related mortality and severe morbidity. These results underscore the significance of health facility performance and health systems strengthening in general on health outcomes.

A higher number of malaria deaths and severe cases was obtained among children less than 5 years. This finding is expected in countries with a stable and intense *P. falciparum* transmission (Müller, 2011) where severe malaria manifests mostly in young children with

less developed immunity, but becomes less common in older children and adults as acquired immunity gives increasing protection (Carneiro et al., 2010).

A limitation of the study is that health facility records underestimate morbidity and mortality in developing countries because most people who fall sick don't seek health care and a number of them die at home. Results from the 2014-15 malaria indicator survey reported only 80% of children less than 5 years old who had a fever sought care and treatment from a formal health facility (Uganda Bureau of Statistics and ICF International, 2015). This proportion is likely to be even higher among adults since treatment seeking is higher among children compared to adults, therefore a large proportion of severe malaria illnesses and deaths occur in people's homes without coming to the attention of a formal health service (World Health Organization, 2016). Our findings are generalizable only for lower level facilities in Uganda namely, HCIIIs and HCIIs, and not for HCIVs and hospitals which serve as referral centers for lower facilities. Furthermore, our estimates for general service and malaria-specific readiness indicators may be overestimated since data on the availability of training guidelines and manuals was not collected in the survey.

6.5 Conclusion

The composite readiness score created by exploiting more than one axis in the multiple correspondence analysis produces a more informative (explains more variation in the original data) and consistent health facility readiness measure that is capable of capturing all aspects of readiness unlike the index based on only the first axis. Higher facility readiness is associated with a reduced risk of severe malaria outcomes in the lower level facilities in Uganda. However, facility readiness to provide malaria treatment services is low. The biggest obstacle hindering lower level health facility readiness is the severe absence of basic amenities and stock-out of essential medicines. If the health facility readiness remains as it is now, the decline of severe malaria burden may be reversed, which will compromise the

achievement of the goals of the Health Sector Strategic and Investment Plan development plan (HSSP) of 2015/16-2019/2020. The government should address lower level facility readiness gaps by increasing health sector funding to the levels recommended by Abuja declaration in order to achieve and sustain a substantial reduction in severe malaria burden in the country.

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6.6 Appendix

A geostatistical negative binomial model (Cressie, 2015) was fitted to assess the effect of the facility readiness index on malaria related deaths (HCIII) or severe malaria cases (HCIII and HCII), separately adjusted for facility characteristics. Let Y_i be the cumulative count of malaria related deaths or severe malaria cases reported by health facility i during January – December 2013. Y_i is assumed to follow a negative binomial distribution, $Y_i \sim NB\ (p_i, r)$ where $p_i = {}^{r}/_{r\ +\ \mu_i}$ and r is the dispersion parameter of the distribution. We relate the predictors to the mean count μ_i of the malaria outcome reported at facility i via the log-linear regression equation, $log(\mu_i) = \log(N_i) + \boldsymbol{\beta}^T \boldsymbol{X} + \omega_i + \varphi_i$ where N_i is the offset which was considered to be the total number of severe malaria cases for the malaria deaths outcome and the total number of confirmed malaria cases for the severe malaria cases outcome. $\boldsymbol{X}$ are the predictors, that is, the facility readiness index and facility characteristics, and $\boldsymbol{\beta}$ is the vector of regression coefficients. ω_i are facility location random effects added in the model to account for spatial dependence in the rates of severe malaria morbidity/mortality. We assumed a Gaussian process on $\boldsymbol{\omega} = (\omega_1, \omega_2, \dots, \omega_k)^T$, that is, $\boldsymbol{\omega} \sim N(0, \sigma^2 R)$ where R is a correlation matrix, defined by an exponential parametric function of the distance d_{ij} between the locations of facilities i and j i.e. $R_{ij} = \exp(-d_{ij}\rho)$. The parameter σ^2 measures the spatial variation and ρ is a smoothing parameter that controls the rate of correlation decay with increasing distance. The range parameter, $\frac{3}{\rho}$ estimates the minimum distance beyond which spatial correlation is negligible. Non-spatial variation is estimated by the location random effects φ_i, which is assumed to be independent and normally distributed with mean 0 and variance σ_φ^2, that is, $\varphi_i \sim N(0, \sigma_\varphi^2)$. Model fit and parameter estimation was performed using Bayesian formulation and Markov Chain Monte Carlo (MCMC) estimation. Model specification was completed by assigning prior distributions to model parameters. An inverse-gamma hyperprior was assigned for the variance σ_φ^2, a gamma distribution for the spatial

smoothing parameter, and non-informative Gaussian distributions for the regression coefficients with mean 0 and variance 100. Model parameters were estimated using MCMC simulation, running a two-chain algorithm with a burn-in of 10,000 iterations followed by 200,000 iterations. Convergence was formally assessed by the Gelman and Rubin diagnostic (Gelman and Rubin, 1992), implemented in CODA.

A2. Multiple correspondence analysis

Let K denote the number binary readiness indicators, N be the number of health facilities and $\boldsymbol{X}_{Nx(2*K)}$ denote the indicator matrix in which the facilities are displayed as rows and each indicator/tracer is represented by the inclusion of two columns $\boldsymbol{I}_{j_k}^{k}$, one per category of the tracer $k = 1, \dots, K$, corresponding to its presence $(j_k = 1)$ or absence $(j_k = 0)$ from the facility. Let $\boldsymbol{P}$ be the matrix $\boldsymbol{P} = \frac{1}{N*K}\boldsymbol{X}$, r and c the vectors of the row and column totals of $\boldsymbol{P}$, respectively, and $\boldsymbol{S}$ the matrix $\boldsymbol{S} = \boldsymbol{D}_r^{-\frac{1}{2}}(\boldsymbol{P} - \boldsymbol{r}\boldsymbol{c}^T)\boldsymbol{D}_r^{-\frac{1}{2}}$ where $\boldsymbol{D}_r = diag\{\boldsymbol{r}\}$ and $\boldsymbol{D}_c = diag\{c\}$. A readiness score F_i^a corresponding to health facility i and based on the a^{th} factorial axis of MCA is defined by $F_i^a = \frac{1}{K}\sum_{k=1}^{K}\sum_{j_k\in\{0,1\}} W_{j_k}^{a,k} I_{j_k,i}^{k}$ where the weights $W_{j_k}^{a,k}$ are the corresponding column standard coordinates of the a^{th} factorial axis, that is, they are elements of the a^{th} column of the matrix $\boldsymbol{D}_c^{-\frac{1}{2}}\boldsymbol{V}$ where $\boldsymbol{V}$ is the right singular vector of $\boldsymbol{S}$. The factorial score of the first axis is then defined by $F_i^1 = \frac{1}{K}\sum_{k=1}^{K}\sum_{j_k\in\{0,1\}} W_{j_k}^{1,k} I_{j_k,i}^{k}$. The variance explained by the a^{th} factorial axis is given by the eigenvalues $\lambda_a = (\boldsymbol{D}_s^{\boldsymbol{2}})_{\boldsymbol{a}}$.

A3. Construction of a composite readiness score

Following the approach proposed by Asselin (2009), for each indicator k we define a discrimination measure Δ_l^a on each factorial axis a, $\Delta_k^a = \sum_{j_k \in \{0,1\}} \frac{n_{j_k}^k}{N} (W_{j_k}^{a,k})^2$ where $n_{j_k}^k$ is the absolute frequency of the j_kth category of indicator k. The average of the discrimination measures across the K indicators on the a^{th} axis corresponds to the total variance explained by the axis, that is, $\lambda_a = \frac{1}{K} \sum_{k=1}^{K} \Delta_k^a$.

For each factorial axis, we split the indicators in two groups, each satisfying the Axis Ordering Consistency condition (AOC) in one of the two axis orientations, i.e. positive (G_1) or negative (G_2). We then calculate the total variance explained by each group in the axis, that is, $\Delta_{G_j}^a = \sum_{k \in G_j} \Delta_k^a$ where $j = 1,2$ and retain on the axis the group of indicators explaining more variation that a threshold T_a which is taken to be 50% of the variance explained by the axis, that is, $T_a = 0.5 * K * \lambda_a$. The groups of indicators retained on the axes, are overlapping and an indicator can be retained on several axes. We remove intersections by selecting the factorial axis with the highest discrimination measure for than indicator among all axes. We define the composite readiness score $F_i = \frac{1}{K} \sum_{k=1}^{K} \sum_{j_k \in \{0,1\}} \sum_{a=1}^{L} \delta(k-a) W_{j_k}^{a,k} I_{j_k,i}^k$ where L is the number of factorial axes used in the composite score and $\delta(k-a)$ is the Dirac delta function which takes the value 1 when the k^{th} indicator is retained on the a^{th} factorial axis and 0 otherwise, that is, $\delta(k-a) = 1$ if $k = a$ and $\delta(k-a) = 0$ if $k \neq a$. To improve interpretation of the score we translate the weights so that the absence category $(j_k = 0)$ of the k indicator to receive a zero weight and the presence one $(j_k = 1)$ to receive a strictly positive representing the gain in the readiness increase measured by the axis a when a facility i acquires the k tracer. Therefore the $W_{j_k}^{a,k}$ in F_i is replaced by $W_{j_k}^{+a,k}$ where $W_0^{+a,k} = 0$ and $W_1^{+a,k} = W_1^{+a,k} - W_0^{a,k}$.

A4. Geostatistical variable selection

To identify the most important readiness indicators related to malaria deaths and severe malaria cases, Bayesian geostatistical variable selection was implemented using stochastic search and adopting a spike and slab prior distributions for the regression coefficients (Chammartin et al., 2013). For every readiness indicator X_k a Bernoulli variable γ_k was introduced with Bernoulli probability π_k corresponding to the inclusion of X_k in the model. For the coefficient β_k, we assume a prior distribution which is mixture of non-informative normal distributions, $\beta_k \sim \delta(\gamma_{k-1})N(0,\tau_k^2) + \big(1-\delta(\gamma_{k-1})\big)N(0,\vartheta_0\tau_k^2)$ where $\delta(.)$ is the Dirac delta function. Therefore, in case X_k is included in the model (slab) and an informative normal prior shrinking β_k to zero (spike) if X_k is included in the model, $\beta_k \sim N(0,\tau_k^2)$ (slab) and in case X_k is excluded, $\beta_k \sim N(0,\vartheta_0\tau_k^2)$ where $\vartheta_0 = 10^5$ is a very large number shrinking the variance to zero i.e. spike component of the prior. We have adopted a $Beta(1,1)$ hyperprior for π_k and an inverse gamma prior for the variance τ_k^2 with mean 1 and variance 10.

Table A6.1: Frequency distribution and chi-square test results of general service and malaria-specific readiness indicators compared by level and facility characteristics

Indicator	Total (N=201) n (%)	Facility level			Managing authority			Location			Distance to district headquarters		
		HCIIIs N=105	HCIIs N=96	P-value	Public N=146	Private N=55	P-value	Rural N=166	Urban N=35	P-value	0-10 km N=52	>10 km N=149	P-value
		n(%)	n(%)		n(%)	n(%)		n(%)	n(%)		n(%)	n(%)	
Basic amenities	**3 (1.5)**	**3 (2.9)**	**0 (0.0)**	**0.095**	**1 (0.7)**	**2 (3.6)**	**0.124**	**1 (0.6)**	**2 (5.7)**	***0.023***	**2 (3.9)**	**1 (0.7)**	**0.104**
Uninterrupted power supply	77 (38.3)	45 (42.9)	32 (33.3)	0.165	56 (36.4)	21 (38.2)	0.982	67 (40.4)	10 (28.6)	0.192	21 (40.4)	56 (37.6)	0.721
Improved water source inside or within source of facility	58 (28.9)	37 (35.2)	21 (21.9)	*0.037*	37 (25.3)	21 (38.2)	0.073	46 (27.7)	12 (34.3)	0.435	19 (36.5)	39 (26.2)	0.156
Access to adequate sanitation facilities for clients	182 (90.6)	94 (89.5)	88 (91.7)	0.604	135 (92.5)	47 (85.5)	0.130	152 (91.6)	30 (85.7)	0.282	45 (86.5)	137 (92.0)	0.251
Communication equipment (phone or short wave radio)	28 (13.9)	22 (21.0)	6 (6.3)	*0.003*	10 (6.9)	18 (32.7)	*<0.0001*	14 (4.8)	14 (40.0)	*<0.0001*	11 (21.2)	17 (11.4)	0.081
Access to computer with email/internet access	29 (14.4)	21 (20.0)	8 (8.3)	*0.019*	12 (8.2)	17 (30.9)	*<0.0001*	16 (9.6)	13 (37.1)	*<0.0001*	11 (21.2)	18 (12.1)	0.109
Emergency transportation	21 (10.5)	16 (15.2)	5 (5.2)	*0.020*	4 (2.7)	17 (30.9)	*<0.0001*	12 (7.2)	9 (25.7)	*0.001*	7 (13.5)	14 (9.4)	0.409
Basic equipment	**101 (50.3)**	**63 (60.0)**	**38 (39.6)**	**0.004**	**63 (43.2)**	**38 (69.1)**	***0.001***	**77 (46.4)**	**24 (68.6)**	***0.017***	**26 (50.0)**	**75 (50.3)**	**0.967**
Adult scale	157 (78.1)	87 (82.9)	70 (72.9)	0.089	106 (72.6)	51 (92.7)	*0.002*	126 (75.9)	31 (88.6)	0.100	36 (69.2)	121 (81.2)	0.072
Child scale	159 (79.1)	89 (84.8)	70 (72.9)	*0.039*	116 (79.5)	43 (78.2)	0.843	132 (79.5)	27 (77.1)	0.753	38 (73.1)	121 (81.2)	0.214
Thermometer	163 (81.1)	88 (83.8)	75 (78.1)	0.304	112 (76.7)	51 (92.7)	*0.010*	129 (77.7)	34 (97.1)	*0.008*	43 (82.7)	120 (80.5)	0.733
Stethoscope	178 (88.6)	98 (93.3)	80 (83.3)	*0.026*	124 (84.9)	54 (98.2)	*0.009*	144 (86.8)	34 (97.1)	0.079	47 (90.4)	131 (87.9)	0.631
Blood pressure apparatus	168 (83.6)	91 (86.7)	77 (80.2)	0.217	119 (81.5)	49 (89.1)	0.196	137 (82.5)	31 (88.6)	0.381	43 (82.7)	125 (83.9)	0.841
Standard precautions for infection prevention	**9 (4.9)**	**5 (4.8)**	**4 (4.2)**	**0.838**	**3 (2.1)**	**6 (10.9)**	***0.007***	**4 (2.4)**	**5 (14.3)**	***0.002***	**3 (5.8)**	**6 (4.0)**	**0.601**
Sterilization equipment	36 (17.9)	29 (27.6)	7 (7.3)	*<0.0001*	18 (12.3)	18 (32.7)	*0.001*	25 (15.1)	11 (31.4)	*0.022*	9 (17.3)	27 (18.1)	0.895
Appropriate storage of sharps waste	194 (96.5)	101 (96.2)	93 (96.9)	0.791	142 (97.3)	52 (94.6)	0.349	161 (97.0)	33 (94.3)	0.428	49 (94.2)	145 (97.3)	0.296
Safe final disposal of sharps	25 (12.4)	15 (14.3)	10 (10.4)	0.406	12 (8.2)	13 (23.6)	*0.003*	20 (12.1)	5 (14.3)	0.715	8 (15.4)	17 (11.4)	0.455
Disposable syringes with disposable needles	194 (96.6)	101 (96.2)	93 (96.9)	0.791	141 (96.6)	53 (96.4)	0.942	159 (95.8)	35 (100.0)	0.216	49 (94.2)	145 (97.3)	0.296
Disposable gloves	192 (95.5)	98 (93.3)	94 (97.9)	0.117	138 (94.5)	54 (98.2)	0.263	159 (95.8)	33 (94.3)	0.697	51 (98.1)	141 (94.6)	0.301
Diagnostic capacity	**40 (19.9)**	**34 (32.4)**	**6 (6.3)**	***<0.0001***	**24 (16.4)**	**16 (29.1)**	***0.045***	**28 (16.9)**	**12 (34.3)**	***0.019***	**14 (26.6)**	**26 (17.5)**	**0.141**
Malaria RDTs	155 (77.1)	83 (79.1)	72 (75.0)	0.495	118 (80.8)	37 (67.3)	*0.041*	134 (80.7)	21 (60.0)	*0.008*	38 (73.1)	117 (78.5)	0.421

Indicator	Total (N=201) n (%)	Facility level			Managing authority			Location			Distance to district headquarters		
		HCIIIs N=105	HCIIs N=96	P-value	Public N=146	Private N=55	P-value	Rural N=166	Urban N=35	P-value	0-10 km N=52	>10 km N=149	P-value
		n(%)	n(%)		n(%)	n(%)		n(%)	n(%)		n(%)	n(%)	
Blood glucose	64 (31.8)	52 (49.5)	12 (12.5)	*<0.0001*	34 (23.3)	30 (54.6)	*<0.0001*	43 (25.9)	21 (60.0)	*<0.0001*	20 (38.5)	44 (29.5)	0.234
HIV diagnostic capacity	126 (62.7)	89 (84.8)	37 (38.5)	*<0.0001*	87 (59.6)	39 (70.9)	0.139	98 (59.0)	28 (80.0)	*0.020*	38 (73.1)	88 (59.1)	0.072
Urine dipstick	88 (43.8)	74 (70.5)	14 (14.6)	*<0.0001*	56 (38.4)	32 (58.2)	*0.012*	67 (40.4)	21 (60.0)	*0.033*	27 (51.9)	61 (40.9)	0.169
Essential medicines	**5 (2.5)**	**5 (4.8)**	**0 (0.0)**	***0.030***	**1 (0.7)**	**4 (7.3)**	***0.008***	**4 (2.41)**	**1 (2.86)**	**0.877**	**0 (0)**	**5 (3.7)**	**0.181**
Amoxicillin syrup/suspension or dispersible tablet	41 (20.4)	24 (22.9)	17 (17.7)	0.366	6 (4.1)	35 (63.6)	*<0.0001*	24 (14.5)	17 (48.6)	*<0.0001*	15 (28.9)	26 (17.5)	0.079
Ampicillin powder for injection	79 (39.3)	72 (68.6)	7 (7.3)	*<0.0001*	61 (41.8)	18 (32.7)	0.241	61 (36.8)	18 (51.4)	0.106	24 (46.2)	55 (36.9)	0.240
Ceftriaxone injection	101 (50.3)	41 (39.1)	60 (62.5)	*0.001*	64 (43.8)	37 (67.3)	*0.003*	81 (48.8)	20 (57.1)	0.369	26 (50.0)	75 (50.3)	0.967
Gentamicin injection	73 (36.3)	52 (49.5)	21 (21.9)	*<0.0001*	32 (21.9)	41 (74.6)	*<0.0001*	53 (31.9)	20 (57.1)	*0.005*	16 (30.8)	57 (38.3)	0.334
Magnesium sulphate injectable	63 (31.3)	58 (55.2)	5 (5.2)	*<0.0001*	51 (34.9)	12 (21.8)	0.074	54 (32.5)	9 (25.7)	0.430	15 (28.9)	48 (32.2)	0.652
Oral rehydration solution	161 (80.1)	87 (82.9)	74 (77.1)	0.306	116 (79.5)	45 (81.8)	0.708	129 (77.7)	32 (91.4)	0.065	42 (80.8)	119 (79.9)	0.888
Oxytocin injection	63 (31.3)	58 (55.2)	5 (5.2)	*<0.0001*	51 (34.9)	12 (21.8)	0.074	54 (32.5)	9 (25.7)	0.430	15 (28.9)	48 (32.2)	0.652
Zinc sulphate tablets, dispersible tablets or syrup	141 (70.2)	77 (73.3)	64 (66.7)	0.302	111 (76.0)	30 (54.6)	0.003	118 (71.1)	23 (65.7)	0.528	38 (73.1)	103 (69.1)	0.592
Malaria service	**53 (26.4)**	**45 (42.9)**	**8 (8.3)**	***<0.0001***	**32 (21.9)**	**21 (38.2)**	***0.020***	**44 (26.5)**	**9 (25.7)**	**0.923**	**13 (25.0)**	**40 (26.9)**	**0.795**
Thermometer	163 (81.1)	88 (83.8)	75 (78.1)	0.304	112 (76.7)	51 (92.7)	*0.010*	129 (77.7)	34 (97.1)	*0.008*	43 (82.7)	120 (80.5)	0.733
Malaria diagnosis by RDT	155 (77.1)	83 (79.1)	72 (75.0)	0.495	118 (80.8)	37 (67.3)	0.041	134 (80.7)	21 (60.0)	*0.008*	38 (73.1)	117 (78.5)	0.421
Malaria diagnosis by microscopy	97 (48.3)	81 (77.1)	16 (16.7)	*<0.0001*	59 (40.4)	38 (69.1)	*<0.0001*	72 (43.4)	25 (71.4)	*0.003*	27 (51.9)	70 (47.0)	0.539
Malaria treatment (ACTs)	174 (86.6)	88 (83.8)	86 (89.6)	0.231	127 (87.0)	47 (85.5)	0.776	146 (88.0)	28 (80.0)	0.210	43 (82.7)	131 (87.9)	0.341
Intermittent preventive treatment (Fancidar)	171 (85.1)	94 (89.5)	77 (80.2)	0.064	127 (87.0)	44 (80.0)	0.215	144 (86.8)	27 (77.1)	0.147	44 (84.6)	127 (85.2)	0.914
Artesunate	7 (3.5)	5 (4.8)	2 (2.1)	0.301	0 (0)	7 (12.7)	*<0.0001*	4 (2.4)	3 (8.6)	0.071	2 (3.9)	5 (3.4)	0.868

Bold: Domain readiness indicators

Italics: Significant values

Table A6.2: Selection of factorial axes included in the composite score for HCIIIs

Indicators	Discrimination measures							Selected axis	Weights[b] $W_1^{+\alpha,k}$
	Factorial axes[a]								
	1	2	3	4	5	6	7		
Improved water source inside or within source	0.075	0.133	0.051	0.126	0.001	**0.435**	0.158	6	4912
Adult scale	0.003	**0.431**	0.136	0.056	0.003	0.014	0.057	2	4656
Disposable gloves	0.047	0.004	0.089	**0.500**	0.034	0.178	0.090	4	8922
Malaria diagnostic capacity	0.045	0.006	0.187	0.001	**0.569**	0.007	0.010	5	5888
Ampicillin powder for injection	**0.342**	0.020	0.166	0.001	0.021	0.002	0.046	1	2628
Ceftriaxone injection	0.001	**0.356**	0.067	0.157	0.192	0.003	0.001	2	3267
Gentamicin injection	0.012	**0.516**	0.021	0.028	0.104	0.038	0.006	2	3839
Magnesium sulphate injectable	**0.811**	0.006	0.135	0.007	0.001	0.003	0.004	1	3777
Oxytocin injection	**0.811**	0.006	0.135	0.007	0.001	0.003	0.004	1	3777
Zinc sulphate tablets	0.188	0.003	0.173	0.082	0.158	0.001	**0.273**	7	4287
Microscopy	**0.194**	0.061	0.082	0.146	0.005	0.184	0.187	1	2188
Variance threshold (T_a)	1.265	0.769	0.622	0.556	0.545	0.435	0.418		
Variation explained ($\Delta_{G_1}^a$)	2.391	1.384	0.478	0.680	0.392	0.005	0.551		
Variation explained ($\Delta_{G_2}^a$)	0.138	0.158	0.764	0.431	0.697	0.863	0.285		
Variation explained after eliminating intersection axis	2.158	1.303	0.000	0.500	0.569	0.435	0.273		

[a]Shaded grey cells (Group 1-positive orientation); Not shaded (Group 2 -negative orientation)
[b]Weights were multiplied by 1000

Table A6.2: Selection of factorial axes included in the composite score for HCIIs

Indicator	Discrimination measures					Selected axis	Weights[b] $W_1^{+\alpha,k}$
	Factorial axes[a]						
	1	2	3	4	5		
Emergency transportation	**0.604**	0.000	0.026	0.001	0.025	1	6779
Child scale	0.045	**0.404**	0.051	0.020	0.295	2	3969
Appropriate storage of sharps waste	0.010	0.261	0.126	0.214	**0.309**	5	10954
Single use standard disposable or auto-disable syringes	0.027	0.011	**0.519**	0.114	0.062	3	12156
Disposable gloves	0.001	0.285	0.048	**0.525**	0.039	4	16125
Glucometer	**0.641**	0.022	0.001	0.055	0.000	1	4695
Amoxicillin syrup/suspension or dispersible tablet	**0.327**	0.190	0.024	0.001	0.047	1	2904
Thermometer	0.090	0.090	**0.338**	0.038	0.071	3	4129
Microscopy	**0.547**	0.020	0.015	0.017	0.000	1	3848
Artesunate	**0.368**	0.017	0.013	0.004	0.001	1	8239
Variance threshold (T_a)	1.330	0.650	0.580	0.495	0.425		
Variation explained ($\Delta_{G_1}^a$)	2.659	0.511	0.280	0.928	0.421		
Variation explained ($\Delta_{G_2}^a$)	0.001	0.788	0.881	0.061	0.428		
Variation explained after eliminating intersection axis	2.487	0.404	0.857	0.525	0.309		

[a]Shaded grey cells (Group 1-positive orientation); Not shaded (Group 2 -negative orientation)
[b]Weights were multiplied by 1000

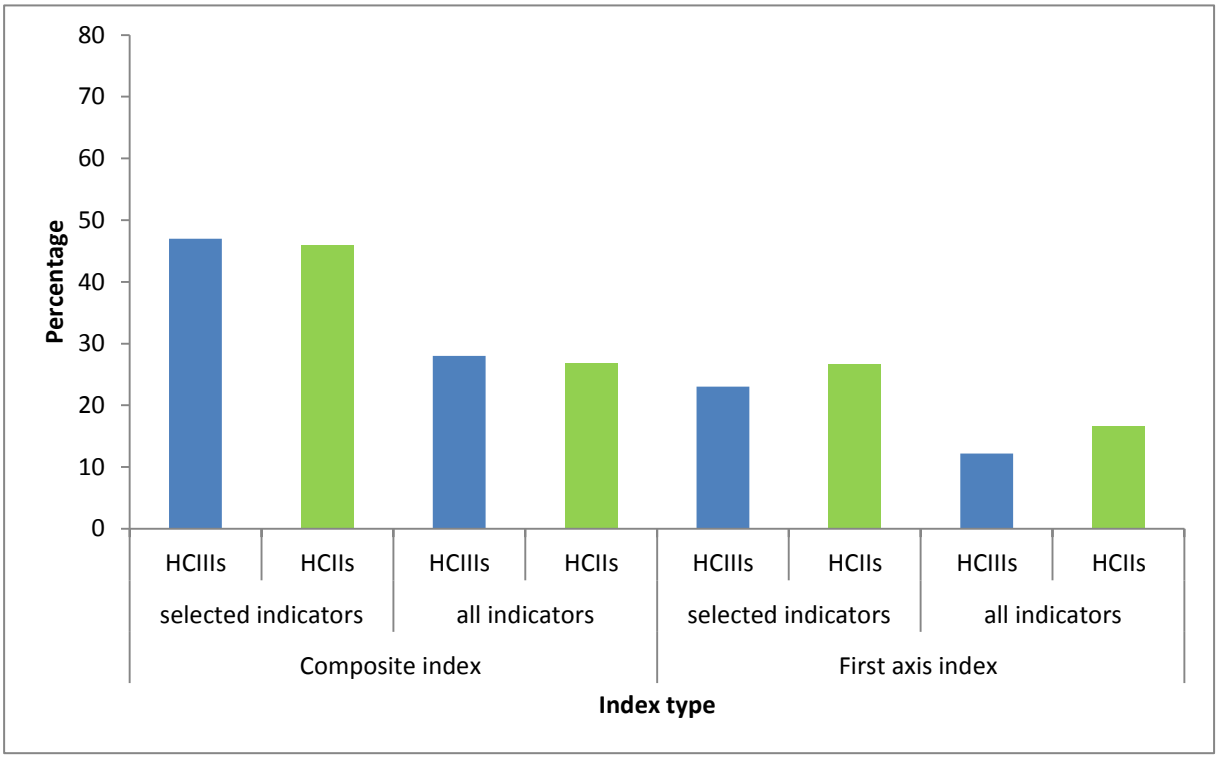

Figure A6.1: Proportion of variation explained by the composite score and the score based on the first factorial axis for HCIIIs (blue) and HCIIs (green)

(a) (b)

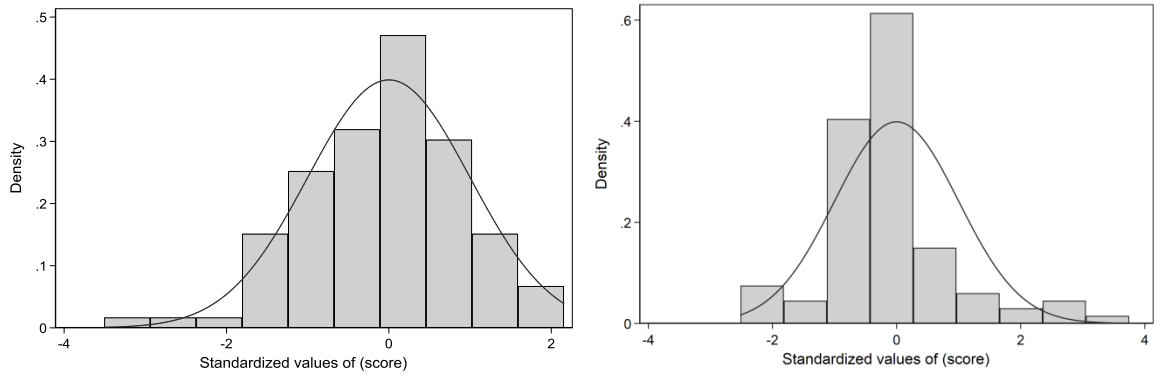

Figure A6.2: Distribution of facility readiness score; HCIIIs (left) and HCIIs (right)

Table A6.3: Posterior estimates of the effects of composite facility readiness index on severe malaria outcomes based on all indicators

Characteristic	HCIIIs		HCIIs
	Malaria deaths	Severe malaria cases	Severe malaria cases
	IRR (95%BCI)[1]	IRR (95%BCI)	IRR (95%BCI)
Readiness index			
Low	1	1	1
Medium	1.96 (0.68, 2.54)	0.29 (0.21, 0.44)*	1.33 (0.58, 1.42)
High	0.65 (0.31, 1.20)	0.44 (0.35, 0.57)*	1.53 (0.91, 1.72)
Location			
Rural	1	1	1
Urban	0.62 (0.22, 0.99)*	1.37 (1.13, 2.02)*	2.48 (1.20, 4.85)*
Ownership			
Government	1	1	1
Private	1.35 (0.83, 1.71)	9.36 (7.00, 11.64)*	3.23 (1.75, 3.93)*
Distance to district headquarters			
<=10km	1	1	1
>10km	0.44 (0.19, 0.86)*	1.27 (0.56, 1.58)	3.98 (3.01, 6.12)*
Spatial parameters			
Spatial variance	0.50 (0.37, 0.60)	0.61 (0.49, 0.99)	0.68 (0.54, 0.87)
Range (km)	5.47 (2.77, 16.64)	4.26 (2.73, 13.21)	35.51 (4.65, 70.31)

**statistically important effect; [1]IRR: Incidence Rate Ratio*

Chapter 7: Towards model-based development of malaria early warning system to predict outbreaks in Uganda

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Abstract

Introduction

The combination of adverse weather conditions in recent times and a declining malaria burden in Uganda due to sustained high intervention coverage has contributed to the occurrence of malaria outbreaks. Planning effective response efforts is however complicated by the absence of a Malaria Early Warning System (MEWS). In this study, we developed highly predictive performance polynomial distributed lag models to forecast malaria outbreaks in different malaria endemic settings of the country.

Methods

Weekly malaria surveillance data from Integrated Disease Surveillance and Response (IDSR) system reported by health facilities during 2013-2016 was modeled using negative binomial models with rainfall, Normalized Difference Vegetation Index (NDVI), day and night Land Surface Temperature (LST) as explanatory variables in polynomial distributed lag models. Stochastic variable selection was used to identify the optimal polynomial function that provides the best model fit. One week out-of-sample approach was used to forecast malaria cases and model predictive performance was assessed by comparing actual and forecasted estimates with their levels of uncertainty.

Results

The third and first order polynomial functions provided the most optimal description of malaria-climatic variability in the low and very high endemic settings, respectively. On the other hand, the second order polynomial function was the optimal model for the moderate and high endemic settings. Models had a high predictive performance in all settings although this differed by setting. Rainfall was associated with a much delayed increase in malaria and immediate decrease in malaria in low and moderate endemic settings, but an immediate increase in malaria in the high and very high endemic settings. Day LST was associated with

an immediate decline in malaria followed by a delayed increase in low, moderate and high endemic settings, but an immediate increase in malaria in very high endemic settings.

Conclusion

The polynomial distributed lag models have a high predictive performance and can serve as a foundation for a model-based Malaria Early Warning System (MEWS) to improve decision-support systems in malaria control and mitigate outcomes from outbreaks.

Key words: Polynomial Distributed Lag Models (PDLMs), malaria forecasting, stochastic variable selection, predictive performance, Malaria Early Warning System (MEWS)

7.1 Introduction

Malaria is the most serious parasitic infection worldwide accounting for over 216 million clinical cases and nearly a half million deaths annually, majority of which occur in sub-Sahara Africa region (World Health Organization, 2016). In Uganda, malaria is caused by *Plasmodium falciparum* and is transmitted primarily by *Anopheles gambiae s.s.* mosquitoes. Transmission is high and stable in the low lands that make 95% of the country (President's Malaria Initiative, 2017). The highlands experience low transmission and are prone to epidemics.

In recent times extreme weather conditions such as floods and long droughts have occurred in different parts of the country leading to the occurrence of malaria outbreaks that have resulted in high morbidity and mortality (National Malaria Control Program, 2016). The current outbreak detection system used by the National Malaria Control Program (NMCP) is a hybrid of one that has been promoted by the World Health Organisation (WHO) for epidemic-prone settings (Global Partnership to Roll Back, 2001). It involves comparing weekly cases reported from the Integrated Disease Surveillance and Response (IDSR) system incorporated in the national Health Management Information System (HMIS) (Cox and Abeku, 2007; Lukwago et al., 2013) with the thresholds defined from historical morbidity data to provide a signal of outbreaks whenever a threshold is exceeded (Cox et al., 2007). This implies that outbreaks are detected long after their occurrence to enable any meaningful intervention efforts in affected areas (Thomson et al., 2006).

The close malaria-climate relationship can be exploited in the design of a model-based Malaria Early Warning System (MEWS) capable of detecting malaria outbreaks before their occurrence (Thomson et al., 1996). This would allow enough time for planning response efforts and mobilization of resources for affected areas to mitigate morbidity and mortality outcomes. Temperature and rainfall are the most important climatic factors for malaria

transmission due to their influence on the duration of development of malaria vectors and parasites (Thomson et al., 2017). Increasing temperature accelerates the rate of mosquito larval development, the frequency of blood feeding by adult females on humans, and reduces the time to maturity of malaria parasites in the gut of female the Anopheles mosquitoes (Bayoh and Lindsay, 2003). Increased rainfall creates and increases breeding sites for mosquitoes, thus increasing their numbers (Thomson et al., 2017). Normalized difference vegetation index (NDVI) – a measure of greenness of the vegetation is a proxy for humidity and rainfall and has been shown to have a high predictive potential for malaria transmission in the tropics (Githeko, 2001).

The malaria-climatic variability relationship was first exploited in the design of a MEWS during the 1990s by linking satellite climatic products with epidemiological and entomological data from the Gambia (Thomson et al., 1996). Since then, several studies have attempted model-based malaria forecasting systems in endemic and epidemic-prone settings (Zinszer et al., 2012). In majority of these studies, statistical approaches majorly a generalized linear model approach to time series analysis was adopted employing the Autoregressive Integrated Moving Average (ARIMA) models and/or Seasonal Auto-Regressive Integrated Moving Average (SARIMA) modeling framework (Abeku et al., 2002; Adimi et al., 2010; Briët et al., 2008; Darkoh et al., 2017; Gomez-Elipe et al., 2007a; Haghdoost et al., 2008; Wangdi et al., 2010; Xiao et al., 2010; Zhang et al., 2010). This framework assumes a linear and one-time relationship between malaria and climatic factors. However, this assumption has been shown not to be correct by laboratory experiments which instead suggest a complex non-linear relationship distributed over time (Bayoh and Lindsay, 2003; Christiansen-Jucht et al., 2015b; Githeko and Ndegwa, 2001b).

Another approach involving the use of polynomial functions has been used in very few studies (Chatterjee and Sarkar, 2009; Teklehaimanot et al., 2004a) to model this complex non-

linear relationship and capture the distributed effect of environmental/climatic factors on malaria. , although has been shown to describe well the complex non-linear relationship between malaria cases and climatic factors. In one particular study conducted in Ethiopia (Teklehaimanot et al., 2004a), polynomial distributed lag models were able to show that the distributed lag effects of climatic factors on malaria cases differed between hot and cold settings, and the results were similar to laboratory experiments findings. Although this methodology is robust for description of malaria-climatic factors relationship given the flexibility of different polynomial functions to describe complex relationships, a need arises to determine the optimal polynomial function suitable for each malaria transmission setting in a country like Uganda with distinct malaria transmission rates (Okello et al., 2006b).

In this study, we developed polynomial distributed lag models to assess the distributed effect of environmental/climatic factors on malaria and forecast malaria cases in different endemic settings in Uganda using weekly surveillance data reported through the IDSR during 2013-2016 and climatic data obtained from remote sensing sources. We employed stochastic variable selection to identify the optimal polynomial order that provide the best description to malaria-climatic factors relationship in each setting in the country.

7.2 Methods

7.2.1 Settings

Uganda is located along the central African rift valley within the Nile basin. It shares borders with Kenya to the east, South Sudan to the north, the Democratic Republic of the Congo to the west, Rwanda to the southwest and Tanzania to the south. The country varies in topography ranging from high altitude areas in the mid-western and eastern parts to the low lying Sudanese plain in the north. The central region is dominated by the large shallow inland Lake Kyoga, L. Victoria and L. Albert. The north eastern region has the driest climate and is prone to droughts. The climate in the south is heavily influenced by L. Victoria that prevents

temperatures from varying significantly while at the same time increases cloudiness and rainfall. The country experiences two rainfall seasons during March–May and September–November.

7.2.2 Outcome

Weekly surveillance parasitologically confirmed malaria cases data reported through the IDSR during January 2013- August 2016 was extracted from the District Health Information System version 2 (DHIS2). The cases were confirmed by Rapid Diagnostic Tests (RDTs) at lower level facilities and either RDTs or microcopy at higher facilities in accordance with the national malaria diagnosis guidelines (National Malaria Control Program, 2016).

7.2.3 Predictors

Day Land Surface Temperature (LSTD), Night Land Surface Temperature (LSTN), and Normalized Difference Vegetation Index (NDVI) were extracted from the Moderate Resolution Imaging Spectroradiometer (MODIS) at a spatial resolution of 1 x 1 km^2 and temporal resolution of 8 days and16 days, respectively. Dekadal rainfall data was obtained from the US early warning and environmental monitoring system at 8 x 8 km^2 resolution (Early Warning and Environmental Monitoring Program, 2016).

7.2.3 Statistical analysis

Weekly climatic factor estimates of LSTD, LSTN and NDVI were calculated by averaging their respective values for a given week. Weekly rainfall was estimated by summing up rainfall amounts of a given week. The climatic data was linked with malaria cases of a particular week, and weeklylags created for climatic data. Since a rainfall season in Uganda lasts for three months and rainfall is the main driver of transmission, lags from the current (week zero) up to 11 weeks were created for the climatic factors.

Weekly malaria cases data was then modeled by a negative binomial regression model formulated in the Bayesian framework in a polynomial distributed lag model. The climatic covariates lags were added in the model as explanatory variables. A negative binomial model was preferred over a Poisson because of its robustness to over dispersion in the malaria data arising out of seasonality.

For each of the climatic covariates, a matrix of dimension 135x12 was created consisting of lagged observations from week zero to week 11. Each covariate data matrix was fitted separately in polynomial models of order 1-4 in each endemic setting and subjected to stochastic variable selection to determine the optimal order with the highest inclusion probability in modeling the distributed effect of climate on malaria. The optimal model in each setting namely, the model with the highest inclusion probability was further used to estimate the distributed lag effect of climatic factors on malaria cases in each setting. Temporal correlation across weeks was captured by weekly random effects modeled by an autoregressive process of order 1. Models were adjusted for seasonality by including Fourier trigonometric terms.

To determine model predictive performance in each endemic setting, the data was segmented into a model building/training and forecast segments. The training segment comprised of 85% and a forecast set consisting of 15% of the time series data. Model predictive performance at each lead time of the forecast data segment was assessed by comparing actual cases and the forecasted estimates summarized from their posterior distribution and the forecast error. The forecast error was expressed as the difference between the forecasted and actual cases divided by actual cases multiplied by 100.

Models were implemented in OpenBUGS and parameters were estimated using Markov Chain Monte Carlo (MCMC) algorithm. An initial burn-in of 10,000 iterations were run on two chains to initialize the models, followed by 500,000 iterations to estimate

parameters. Model convergence was assessed by the Gelman and Rubin convergence statistics (Raftery and Lewis, 1992). Parameters were summarized by their posterior medians and 95% Bayesian Credible intervals (BCIs).

7.3 Results

7.3.1 Descriptive results

Table 7.1 and Figure 7.1 present a summary of average weekly malaria incidence and its distribution, and climatic factors for the 10 regions classified in different endemicity groups. Results indicate that malaria burden in the country largely fall into four distinct groups consisting of low endemicity (<2.0 cases per 1000 persons per week), moderate endemicity (2.01-3.50 cases per 1000), high endemicity (3.51-5.00 cases per 1000), and very high endemicity (>5.0 cases per 1000). Overall a total of 22,786,228 malaria cases were reported during the study period, equivalent to a weekly average of 168,787 cases (95%CI: 149 456-188 118).

Table 7.1: Mean weekly summaries of malaria incidence and climatic factors during 2013-2016

Region	Incidence (cases per 1000 persons per week	Rainfall (mm)	NDVI	LSTD (^{o}C)	LSTN (^{o}C)	Endemicity group
Kampala	1.56	31.9	0.36	26.1	19.2	Low
Central 1	2.97	32.4	0.53	26.7	16.9	Moderate
Central 2	3.19	36.4	0.56	27.0	17.3	Moderate
East central	3.19	36.7	0.46	27.7	18.6	High
Mid North	5.89	36.4	0.45	34.2	17.8	Very high
Mid-Western	4.15	34.5	0.59	28.7	16.7	High
Mid-Eastern	4.98	37.2	0.53	32.0	17.7	High
North East	5.86	33.5	0.42	35.9	18.8	Very High
South Western	3.47	29.3	0.60	27.7	15.9	Moderate
West Nile	8.08	39.8	0.44	34.1	19.5	Very High

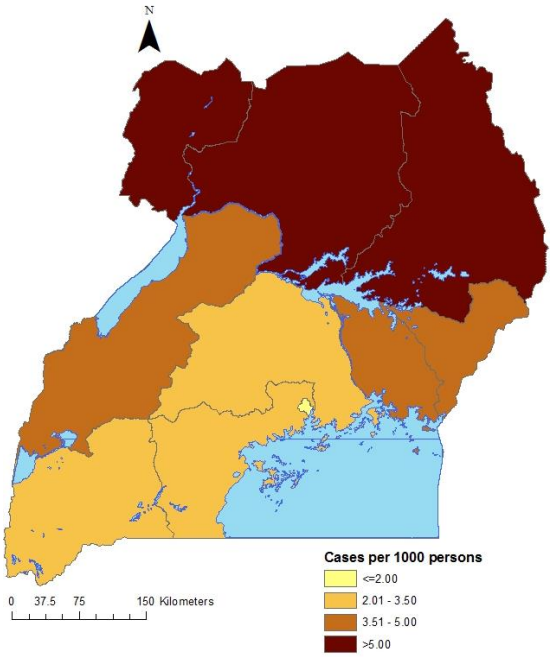

Figure 7.1: Geographical distribution of average weekly malaria incidence

Figure 7.2 depicts temporal trends of weekly malaria incidence for each endemicity setting. The trends are marked by a bi-annual seasonality pattern in each year. The plot also indicates that incidence initially declined up to 2015 in all settings, and after increased except in the low endemic settings where the burden remained nearly constant throughout the period. At all times, incidence was highest and lowest in the very high endemicity and lowest endemicity settings, respectively.

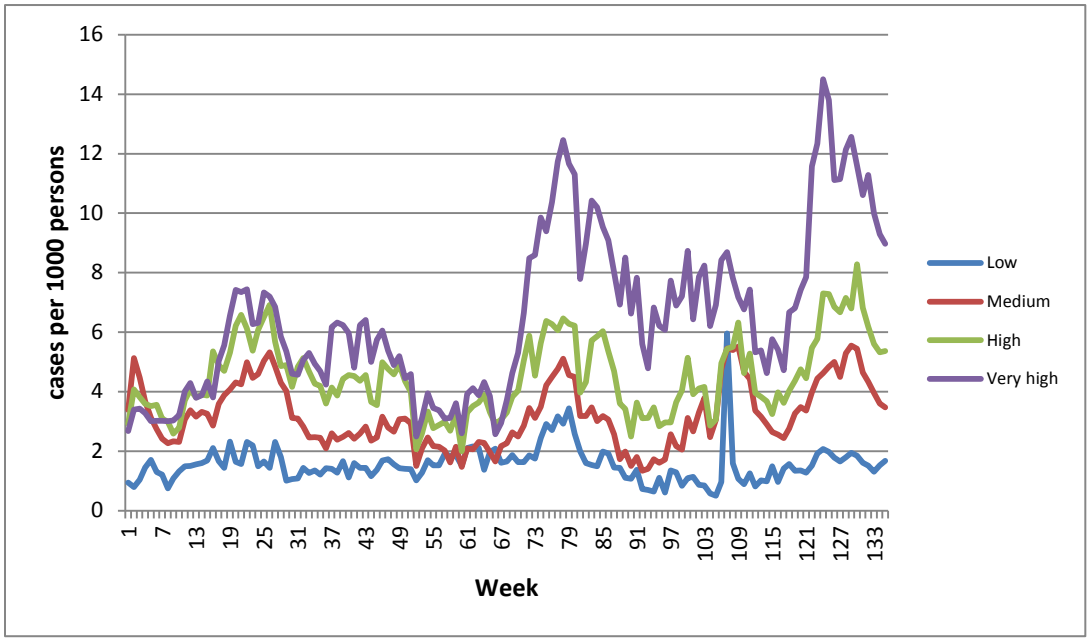

Figure 7.2: Temporal variation of weekly malaria incidence

The temporal variation of climatic factors is presented in Figure 7.3 for all and show similar patterns except for NDVI in the low endemic setting. The unique NDVI temporal trend in this setting is due to the scanty vegetation cover in the capital city (Kampala) which single-handedly makes up this setting. The rainfall intensity differed slightly across settings but the trends in all settings were marked by two peaks during the year. Although, the temporal trends of LSTD and LSTN were similar across all settings, the highest weekly LSTD and maximum variation between LSTD and LSTN were observed in high endemicity settings. The least LSTN was observed in the moderate endemicity settings. The highest NDVI was observed in the moderate and high endemicity settings, while the least was observed in the low endemicity settings.

Pearson correlation coefficient results of the relationship between weekly incidence and climatic covariates at weekly lags up to lag of week 11 are shown in Figure 7.3 in all

endemic zones of the country. Results show a non-linear relationship in all settings which indicates the inadequacy of a linear and a cross-sectional model to describe this relationship.

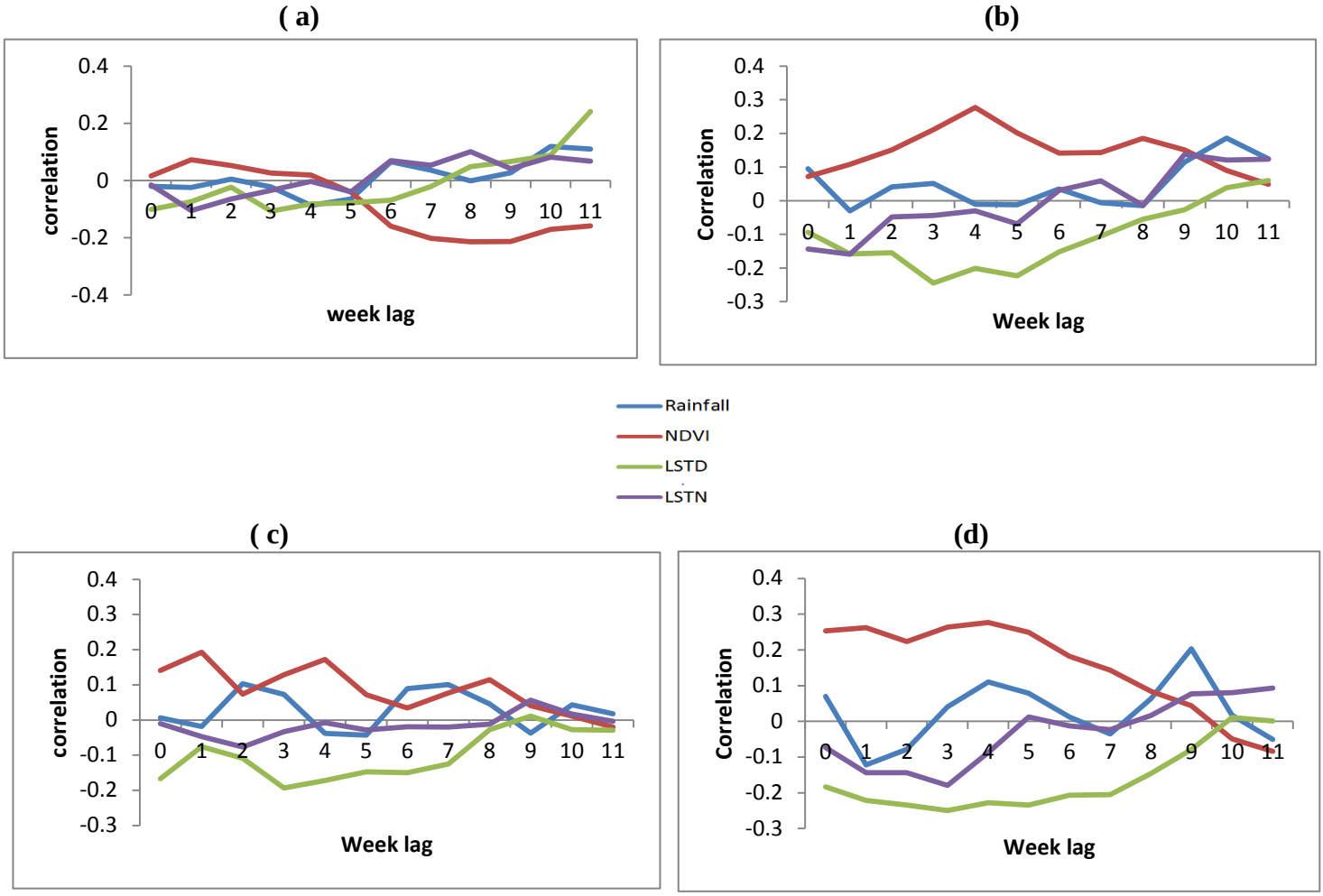

Figure 7.3: Pearson correlation: malaria incidence vs climatic factors; a) Low, b) Moderate, c) High, d) Very high

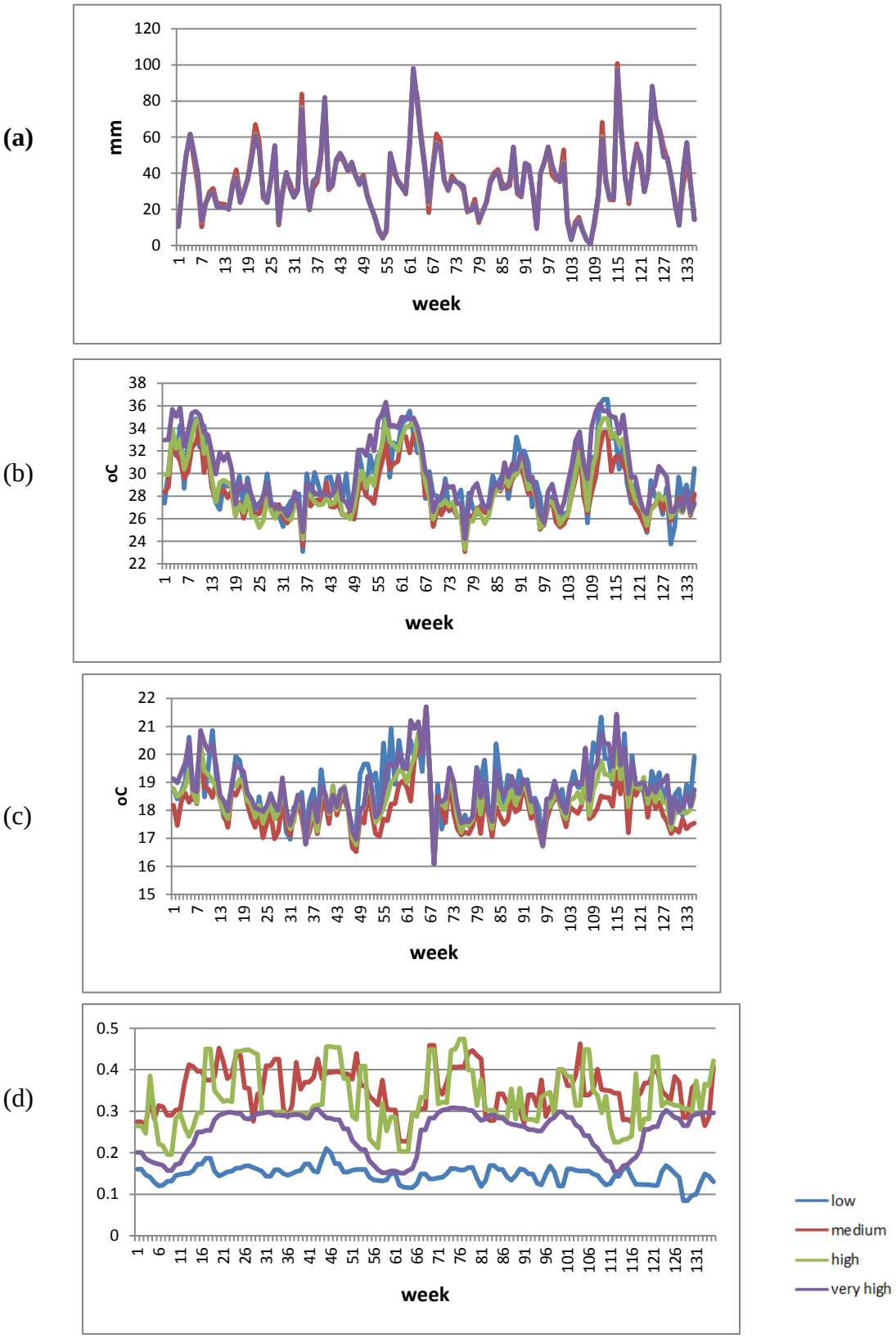

Figure 7.4: Temporal variation of weekly average of climatic factors; a) Rainfall, b) LSTD, c) LSTN, d) NDVI

7.3.2 Stochastic variable selection

Table 7.2 presents stochastic variable selection results for each polynomial model order of climatic factors in each endemic setting. Results indicate higher probabilities of inclusion for the second-order polynomial model in moderate and high endemic settings for most covariates. On the other hand, the third and first polynomial model orders were selected with higher inclusion probabilities for all covariates in the low and very high endemic settings.

Table 7.2: Posterior inclusion probabilities for climatic factors per endemic setting

Endemicity setting	Covariate	Polynomial model order	Probability of inclusion (%)
Low	Rainfall	1	0.2
		2	4.1
		3	32.5*
		4	1.1
	NDVI	1	0.7
		2	21.5
		3	32.5*
		4	9.8
	LSTD	1	23.4
		2	25.7
		3	35.9*
		4	0.1
	LSTN	1	0.5
		2	15.0
		3	29.3*
		4	1.7
Moderate	Rainfall	1	11.2
		2	49.3
		3	32.1*
		4	4.0
	NDVI	1	6.0
		2	40.8*
		3	28.4
		4	5.8
	LSTD	1	14.5
		2	50.1*
		3	23.9
		4	9.0
	LSTN	1	4.7
		2	47.1*
		3	12.2
		4	2.5
High	Rainfall	1	17.2
		2	38.0*
		3	19.4
		4	16.6
	NDVI	1	20.2
		2	48.1*
		3	22.7

		4	6.1
	LSTD	1	6.0
		2	32.0
		3	33.2*
		4	7.9
	LSTN	1	20.7
		2	29.5*
		3	19.5
		4	10.8
Very high	Rainfall	1	62.5*
		2	12.3
		3	9.1
		4	14.9
	NDVI	1	39.9*
		2	20.2
		3	16.5
		4	13.8
	LSTD	1	41.6*
		2	28.4
		3	19.1
		4	2.0
	LSTN	1	35.7*
		2	21.6
		3	4.1
		4	0.1

***Highest inclusion probability*

7.3.3 Distributed lag effect of climatic factors on malaria cases

Figures 7.5 and 7.6 present climatic factor coefficient estimates and their 95% BCIs of the distributed lag effect on malaria incidence in all the four endemic settings estimated from the polynomial distributed lag models identified from stochastic variable selection above.

Results of the distributed lag effect of rainfall on malaria incidence are shown in Figures 7.5a, 7.5b, 7.6a and 7.6b in the low, moderate, high, and very high endemic settings, respectively. Coefficients represent the multiplicative effect of one-millimeter increase in rainfall at a given lag on the incidence of malaria in a given week.

In all settings, results manifest a statistically important effect of rainfall on malaria at most week lags, but the magnitude and direction vary at different lags in different endemic settings. In the low endemic settings, rainfall had a negative effect on malaria incidence at shorter lags (weeks 0-2), no effect at lags three and four, a positive effect at lags five, six, seven and eight, but no effect at longer lags. On the other hand, in the moderate endemic

settings, rainfall had a negative association with malaria incidence from the lag of week zero up to lag of week eight, but the effect is statistically important between lags of week three and week six, a positive effect albeit unimportant from lag nine onwards becoming important at lag 11. In the high endemic settings (Figure 7.5a), the effect is positive throughout but smaller and unimportant from the lag of week zero up to the lag of week five, then from lag of week six on wards it becomes statistically important. In the very high endemic settings, rainfall effect was important and positive at shorter lags but became negative at longer lags (Figure 7.6b).

The effect of NDVI on malaria incidence also varied in different endemic settings. The effect had a sinusoidal shape in the low endemic settings (Figure 7.5c). The effect is only important but negative at lag zero and from lags of week six to 10. In the moderate settings, the effect is negative and important up to lag of week three, but becomes positive from lag of week five onwards (Figure 7.5d). In the high endemic settings (Figure 7.5c), NDVI´s effect is statistically important at shorter lags (weeks 0-1) and longer lags (weeks 9-11), but a negative albeit important effect at lags of week three to eight. On the other hand, NDVI has a decreasing statistically important positive effect in the very high endemic settings (Figure 7.6d).

The effect of day land surface temperature on malaria cases is shown in figures 7.5e, 7.5f, 7.6e and 7.6f. Results are presented as coefficients which indicate an increase in malaria incidence associated with an increase in temperature by one Celsius degree. The effect in the low endemic settings (Figure 7.5e) is negative and statistically important at shorter lags and lag of week 11, but positive between lags of week three to week nine with its maximum effect at the lag of week six. In moderate endemic settings, the effect is entirely negative but increases from the lag of week zero reaching its maximum at the lag of week six but then declines at longer lags (Figure 7.5f). Meanwhile, the effect of LSTD in the high endemic

settings is negative and only important from the lag of week zero to week six (Figure 7.6e). However, LSTD effect increases with increasing lags in the very high endemic settings (Figure 7.6f).

Similarly, results of the effect of night land surface temperature shown in figures 7.5g, 7.5h, 7.6g, and 7.6h represent an increase in malaria incidence associated with an increase in temperature by one Celsius degree. In low endemic settings, LSTN effect is positive at shorter lags and negative at longer lags (Figure 7.5g). In the moderate endemic settings, the effect is positive initially increasing up to the maximum at the lag of week six but declines at longer lags (Figure 7.5h). LTSN has an almost linear relationship that decreases with increasing lag; positive between lag of week zero and week five, and negative from lags of week seven to 11 (Figure 7.5g). In the very high endemic settings, the effect is negative at all lags but statistically unimportant at longer lags (Figure 7.5h).

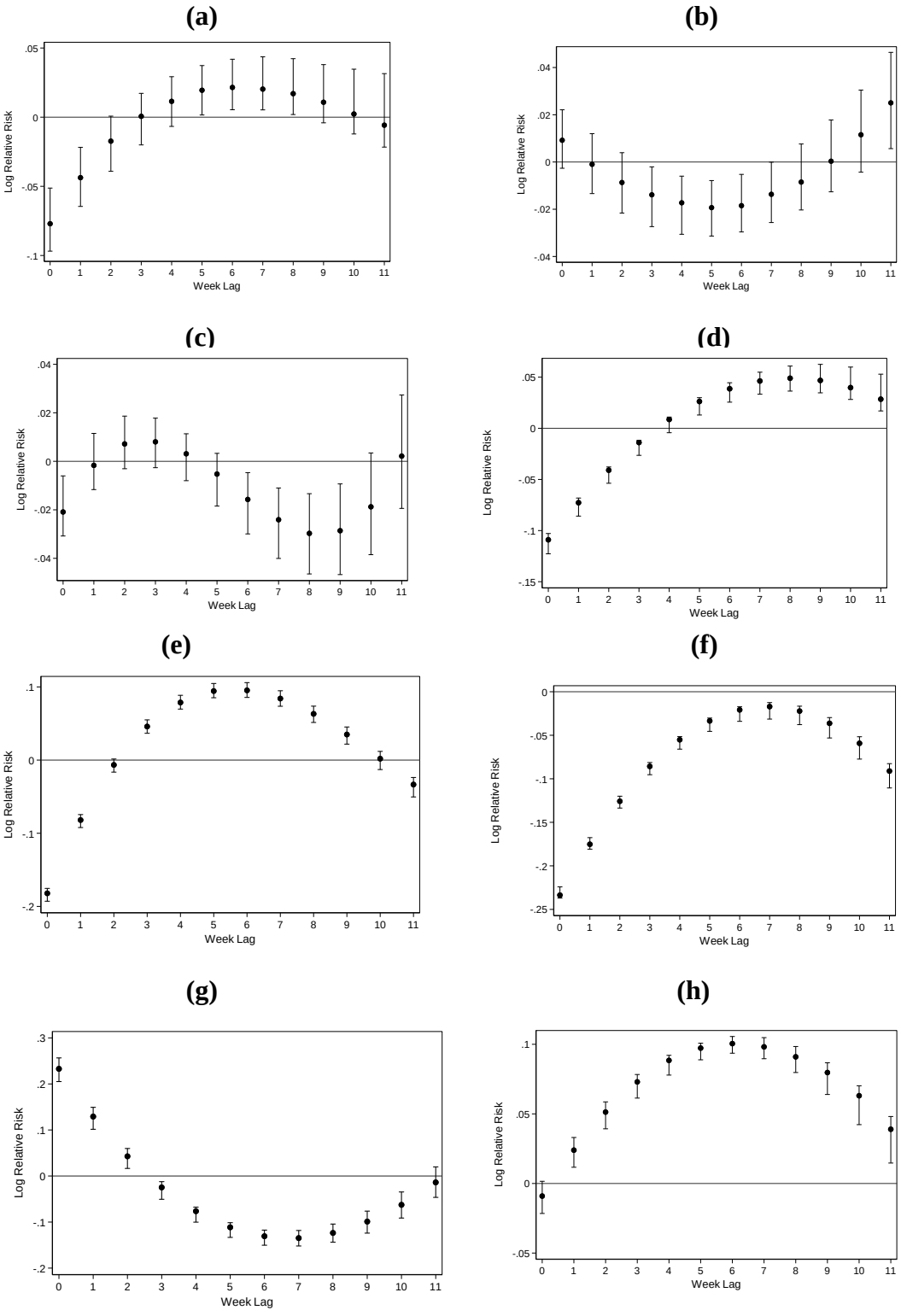

Figure 7.4: Distributed climatic covariates' lag effect in low endemicity (left) and moderate endemicity settings (right); rainfall (a and b), NDVI (c and d) LSTD (e and f) and LSTN (g and h)

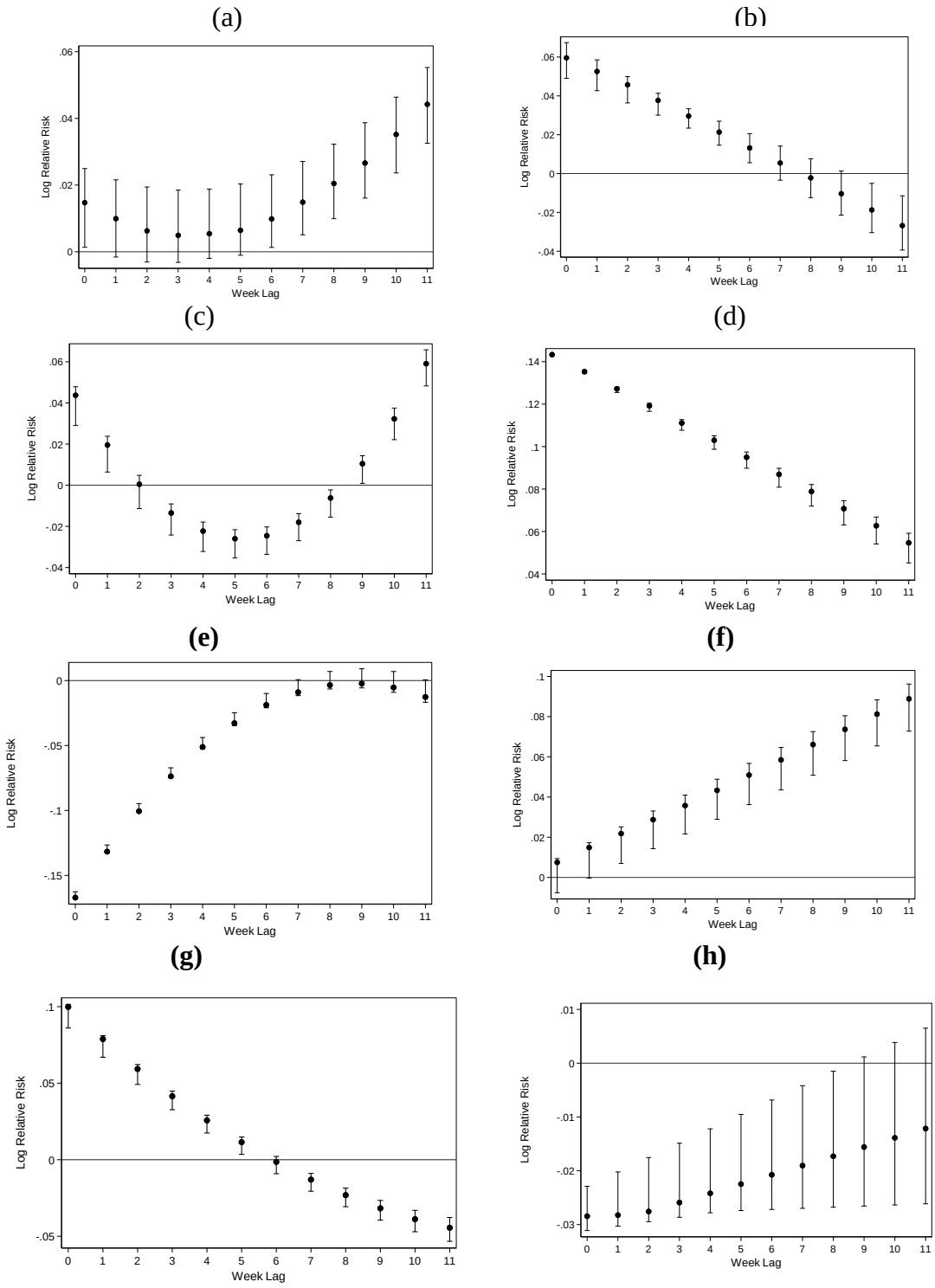

Figure 7.5: Distributed climatic covariates' lag effect in high endemicity (left) and very high endemic settings (right); rainfall (a and b), NDVI (c and d) LSTD (e and f) and LSTN (g and h)

7.3.4 Model predictive performance

Results of the model predictive performance assessed using a one-week out-of-sample approach are shown in Figure 7.6 comparing the number of actual cases and the forecasted estimates and their 95%BCI on the primary axis, and the forecast error on the secondary axis.

The plots show a high predictive performance in all settings but overall the best predictive performance at all lead times was estimated in the moderate endemicity settings with a forecast error of less than 5% for all lead times except for the last week (Figure 7.6b). On the other hand, the lowest predictive performance was observed in the very high endemicity settings with seven out of 20 lead times exceeding 5% forecast error (Figure 7.6d). The highest predictive performance was obtained at lead times of 15, six, seven, and 24 weeks, for low, moderate, high, and very high endemic settings, respectively.

In Figure 7.7, plots of the actual number of malaria cases, fitted, and forecasted cases are shown for each endemic setting at all lead times of the forecast segment. In addition to models having a high predictive performance, plots manifest the suitability of the models in fitting the data well as observed from the closeness of the actual cases series to fitted and forecasted series.

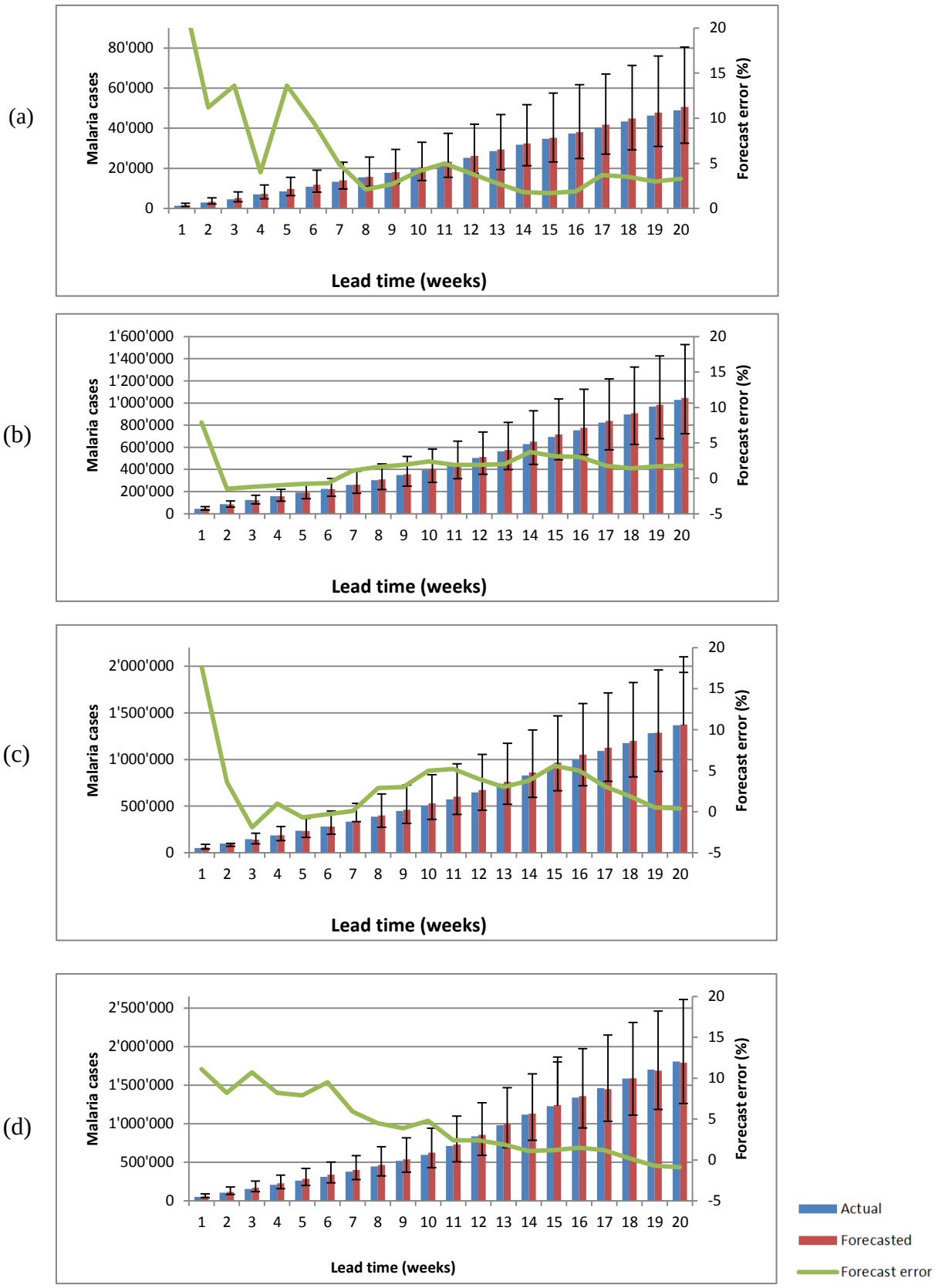

Figure 7.6: Model predictive performance for each lead time of the forecasting data segment a) low endemicity, b) moderate endemicity, c) high endemicity, and d) very high endemicity settings

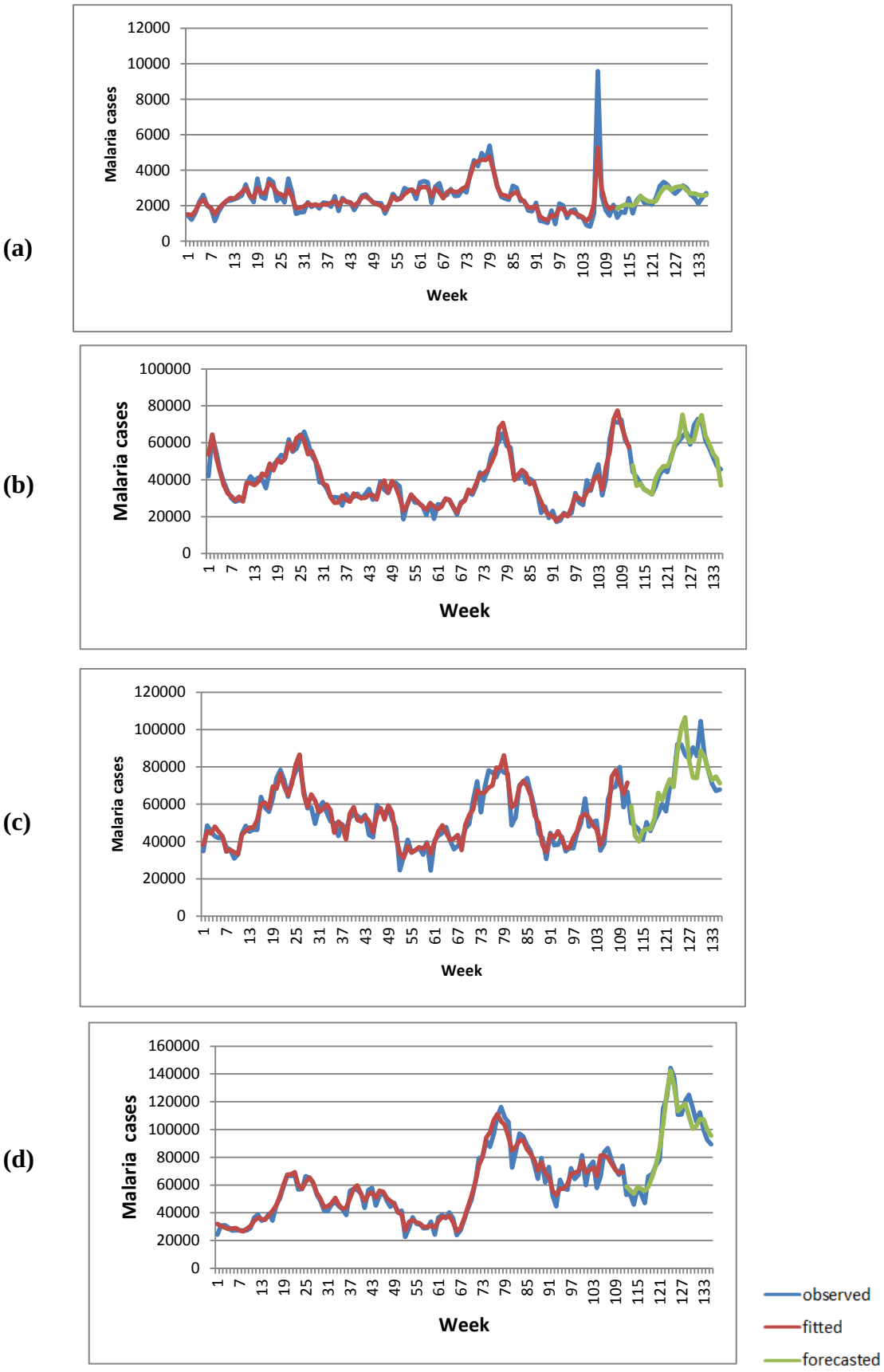

Figure 7.7: Overall model fitting and predictive performance in the four endemic settings; a) low, b) moderate, c) high d) very high (Red, blue and green lines represent actual cases, fitted cased and forecasted cases, respectively)

7.4 Discussion

In this study, we developed highly predictive performance polynomial distributed lag models to forecast malaria outbreaks in different malaria endemic settings in Uganda. We also assessed the distributed lag effect of climatic factors on the incidence of malaria cases and predictive performance at different lead times in each endemic setting.

The study results show that the malaria burden in the country is heterogeneously distributed with the northern-based regions bearing the heaviest burden, while the regions in the central and south-western areas shoulder a low burden. These findings agree with the regional parasitaemia prevalence estimates measured in the malaria indicator surveys (Uganda Bureau of Statistics and ICF International, 2015, 2010) and entomological inoculation rates measured from field studies (Kilama et al., 2014; Okello et al., 2006a). The apparent differences in malaria endemicity between the north of the country and other regions have been attributed to war/civil disturbances in the north, differences in ecological conditions, disparities in socio-economic development, urbanization, and access to health services (Ssempiira et al., 2017d, 2017c). Also, socio-economic practices practiced in this region such as nomadic pastoralism increase the exposure of these populations to a higher malaria risk.

The incidence pattern is characterized by a bi-annual seasonality cycle with peaks coinciding with the two rainfall seasons. This finding suggests a close relationship between rainfall and malaria transmission and supports its inclusion in the forecasting of malaria outbreaks as has been done in other endemic and epidemic-prone settings such as in Kenya (Githeko and Ndegwa, 2001b), Ethiopia (Teklehaimanot et al., 2004b), Botswana (Thomson et al., 2005b), Burundi (Gomez-Elipe et al., 2007b), and Sri Lanka (Briët et al., 2008).

The observed malaria decline up until the weeks of the third quarter of 2015 is similar to results based on parasitaemia prevalence during 2009-2014 (Ssempiira et al., 2017c). This decline has been attributed to the effects of vector control interventions and prompt case

management with artemisinin-based combination therapies (Ssempiira et al., 2017c). The unexpected upsurge of the burden starting in the weeks towards the end of 2015 may be attributed to the reduced immunity resulting from interrupted malaria transmission dynamics (National Malaria Control Program, 2016), development of resistance to the insecticides (Bukirwa et al., 2009), and changes in climate/rainfall leading to increases in exposure to malaria vectors (Jagannathan et al., 2012).

Study results adduced to evidence of a non-linear relationship between malaria and climatic factors in all endemic settings. Indeed this relationship was best described by polynomial functions of varying order in different endemic settings. The suitability of higher order polynomial models in less endemic settings suggests a need for complex modeling framework in less burden settings such as those in pre-elimination and elimination stages. The possible reason for this observation could be the reduced environmental influential on malaria as the disease burden declines as other non-environmental factors become influential. This finding is consistent with the WHO guidelines which prioritize surveillance as a core function and incorporation of mathematical modeling to understand transmission dynamics in countries close to elimination (World Health Organization, 2016). These findings mirror those reported by Thomson et al., 2005 (Thomson et al., 2005b) from a study conducted in Botswana.

Model predictive performance in our study was generally high in all settings, and this could be attributed to the flexibility of the polynomial functions to describe the non-linear complex relationship between climatic factors and malaria as has been reported from field experiments (Bayoh and Lindsay, 2003; Christiansen-Jucht et al., 2014, 2015b). In addition, the Bayesian framework we used in our study is flexible and makes prediction/forecasting straight forward in form of posterior distributions complete with levels of uncertainty. The estimated probabilistic forecasts provide a more robust measure in spite of the shorter time

series data, which outperform forecasts based on likelihood estimation whose predictive power diminishes with fewer time points in the time series (Thomson et al., 2006).

More so, our study employed stochastic variable selection to identify the optimal polynomial function in each endemic setting that best described the malaria-climate relationship. To the best of our knowledge, this is the first malaria forecasting study in which this model penalizing technique has been applied to decide empirically the best model in each setting.

Our results further showed that model predictive performance was lower in the low and very high endemic settings compared to moderate and high endemic settings. This again can be linked to climatic factors having a reduced influence on malaria transmission in very low endemic settings. In case of the very high transmission settings where the risk is stable and perennial, other factors such as low socio-economic development, limited access to health facilities, and low housing standards may explain a sizable variation in the risk compared to that explained by climatic variability (Nájera et al., 1998).

Furthermore, our results manifest a statistically important distributed effect of rainfall in all endemic settings, though the magnitude and direction vary at different lags. Rainfall was associated with a much-delayed increase in malaria incidence and immediate decrease in the low and medium settings, and an immediate increase in malaria in the high and very high endemic settings. Rainfall is important for malaria transmission as it creates breeding sites for mosquitoes which leads to higher numbers of juvenile and adult mosquitoes, as well as increases humidity which favors vector development (Thomson et al., 2006). However, the relationship of malaria with rainfall is non-linear with excess rainfall sometimes being associated with a reduction in malaria (Lindsay et al., 2000), plus the fact that its effect is moderated with its interaction with temperature (Teklehaimanot et al., 2004b). The very high endemic settings consist of regions that experience the highest temperatures. These accelerate

the aquatic stages of mosquitoes and the sporogony cycle leading to an earlier appearance of malaria cases following rainfall unlike the moderate temperatures (<=28^{o}C) experienced in the very low and moderate endemic settings. Under these temperatures, the aquatic stages of mosquito and the sporogony cycle will take longer up to 12 and 8 days, respectively (Bayoh and Lindsay, 2003) causing a longer lag prior to the occurrence of malaria. Our results are in agreement with findings reported by Teklemainahot in Ethiopia (Teklehaimanot et al., 2004b) and also reflect the non-linear relationship reported from other studies (Lindblade et al., 1999; Lindsay et al., 2000; Thomson et al., 2005b).

The effect of NDVI on malaria also varied with settings. NDVI is highly related with rainfall in areas where the natural environment has been preserved, and therefore the effect of both on malaria should be similar. In our study, however, the similarity was only observed in moderate endemic settings probably owing to scanty natural vegetation in the urban region of Kampala that make up the low endemic settings. The decreasing lag effect of NDVI with increasing lag in very high endemic settings was at odds with the rainfall effect in these settings. The probable explanation for this anomaly could be the long dry seasons experienced in these settings due to their savannah vegetation cover. Heavy rainfall usually follows at the end of these extended dry seasons leading to a rapid growth of the vegetation cover while at the same time flooding mosquito breeding sites resulting in reduced transmission and incidence. Comparable findings have been reported in semi-arid settings in Afghanistan (Adimi et al., 2010).

Day land surface temperature was associated with an immediate decline in malaria followed by a delayed increase in the low, moderate and high endemic settings, but an immediate increase in malaria in very high endemic settings. Although these findings do not appear exactly the same as those observed in experiments under controlled conditions, the pattern is similar. The delayed effect of about four weeks before an increase in malaria

observed in the low, moderate and high endemic settings is explained by the 12 and 8 days required for development of aquatic stages of mosquito and the sporogony cycle at 28^{o}C (Bayoh and Lindsay, 2003; Christiansen-Jucht et al., 2015b; Teklehaimanot et al., 2004b). On the other hand, the expected immediate increase in malaria in very high endemic settings supports evidence that high temperatures accelerate the development of the mosquitoes vector, reduces the duration of the sporogonic cycle and the time between feeding intervals (Thomson et al., 2017).

The effect of LSTN was associated with an immediate increase in malaria and a delayed decline in the low, moderate and high endemic settings. Given the prevailing temperatures in these settings, these findings are supported by laboratory experiments (Bayoh and Lindsay, 2003; Christiansen-Jucht et al., 2014, 2015b). However, the relationship in very high settings is not easy to explain since increases in temperature are associated with a decrease in cases which is not supported by any scientific evidence.

The limitation to this study is that the effect of other important malaria risk confounders such as socioeconomic status and interventions were not adjusted for in the models. This is because adjusting for confounders in polynomial distributed lag models complicate interpretations of coefficients.

7.5 Conclusions

We have exploited the close malaria-climatic variability relationship to develop polynomial distributed lag models to forecast malaria outbreaks in different endemic settings in Uganda. These models have a high predictive ability and thus can serve NMCP as a foundation for a model-based malaria early warning system to improve decision-support systems in malaria control. This will address the problem of delayed outbreak detection and improve resource allocation and timely deployment of interventions in areas where outbreaks are detected to mitigate morbidity and mortality outcomes.

The varying degrees of malaria burden in the country and different order of polynomial models feasible in each setting calls for a decentralized MEWS that takes into consideration the local endemicity levels and ecological settings. The success of this system will depend on the close coordination of the NMCP with the IDSR unit, the meteorological department to support remote sensing capabilities, and the district health teams responsible for actual implementation of malaria outbreak response activities. The incorporation of this modeling framework in the MEWS will enhance surveillance contribute to the achievement of the goals in the national and international malaria control, prevention and elimination frameworks.

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7.6 Appendix

Polynomial distributed lag model formulation

Let y_t be the number of aggregated malaria cases from all health facilities reported through the IDRS in week *t=1,…,135*. Y_t is assumed to follow a negative binomial distribution, $y_t \sim NB(p_t, r)$ where $p_t = \frac{r}{r+\mu_t}$; where r is the dispersion parameter and μ_t is the average number of malaria cases in the country. Eleven lags were created for each climatic covariate equivalent to a duration of three months – the typical rainfall season.

The model is formulated with a log link as shown below;

$$\log(\mu_t) = \log(N_t) + f(t) + \alpha + \sum_{i=0}^{11} \beta_i Rain_{t-i} + \sum_{i=0}^{11} \gamma_i NDVI_{t-i} + \sum_{i=0}^{11} \delta_i LSTD_{t-i} + \sum_{i=0}^{11} \theta_i LSTN_{t-i} + \epsilon_{(i-1)*52+t} \quad (1),$$

where N_t is the week population offset in week t obtained from the 2014 national housing and population census data and corrected for population growth (UBOS 2014). α is the intercept, $Rain_{t-i}$, $NDVI_{t-i}$, $LSTD_{t-i}$ and $LSTN_{t-i}$ denote the weekly averages of Rainfall, NDVI, LSTD and LSTN *i* weeks previously, β_i, γ_i, δ_i, and θ_i are the lag weights representing the effect of Rainfall, NDVI, LSTD and LSTN, respectively on current malaria cases y_t. $f(t)$ is the parameter modeling seasonality of malaria incidence, $\epsilon_{(i-1)*52+t}$ are weekly random effects modeled by a first order autoregressive process with temporal variance σ_1^2, that is, $\epsilon_l \sim AR(1)$ where $\epsilon_1 \sim N\left(0, \frac{\sigma^2}{1-\rho^2}\right)$, $\epsilon_l \sim N(\rho\epsilon_{l-1}, \sigma^2), l = 2, \ldots, 135$ and the autocorrelation parameter ρ quantifies the degree of dependence between successive weeks. The seasonal pattern $f(t)$ was captured by a mixture of two harmonic cycles with periods $T_1 = 26$ and $T_1 = 52$ weeks, respectively, that is, $f(t) = \sum_{j=1}^{2} A_j \cos\left(\frac{2\pi}{T_j} t - \varphi_j\right) = \sum_{j=1}^{2} \{a_j * cos\left(\frac{2\pi}{T_j} t\right) + b_j * \sin(\frac{2\pi}{T_j} t)\}$, where t is time in weeks. A_j is the amplitude of the jth cycle

and estimates the incidence peak by the expression $A_j = \sqrt{a_j^2 + b_j^2}$. $\varphi_j$is the phase which is the point where the peak occurs estimated as $\varphi_j = \arctan\left(\frac{a_j}{b_j}\right)$, a_j and b_j are model parameters.The cumulative effect of a unit increase in any of the climatic covariates is the sum of the coefficients/ lag weights (β_i, γ_i, δ_i, and θ_i).

The model in equation (1) has a 12 lag exposure variables for each climatic covariate resulting in a total of 48 coefficients to be estimated. Also, the lags of exposure variables are highly correlated, and this would lead to multicollineraity resulting in unreliable coefficient with large variances and standard errors. To address these constraints, we restricted the lag coefficients using polynomial distributed lags of order 1-4. The n-th order polynomial distributed lags for rainfall, NDVI, LSTD and LSTN were expressed as follows;

Rainfall; $\beta_i = \emptyset_0 + \emptyset_1 i + \emptyset_2 i^2 +, \ldots, + \emptyset_n i^n = \sum_d^n \emptyset_n i^n$

NDVI; $\gamma_i = \rho_0 + \rho_1 i + \rho_2 i^2 +, \ldots, + \rho_n i^n = \sum_d^n \rho_n i^n$

LSTD; $\delta_i = \pi_0 + \pi_1 i + \pi_2 i^2 +, \ldots, + \pi_n i^n = \sum_d^n \pi_n i^n$

LSTN; $\theta_i = \tau_0 + \tau_1 i + \tau_2 i^2 +, \ldots, + \tau_n i^n = \sum_d^n \tau_n i^n,$

where $\emptyset_n$, ρ_n, π_n and τ_n are the parameters of the nth polynomial function describing the lag weights.

The full polynomial distributed lag model of nth order and 11 lags was derived by substituting the expressions above in equation 1;

$$\log(\mu_t) = \log(N_t) + f(t) + \alpha + \sum_{i=0}^{11}(\sum_d^n \emptyset_n i^n)\, Rain_{t-i} + \sum_{i=0}^{11}(\sum_d^n \rho_n i^n)\, NDVI_{t-i} + \sum_{i=0}^{11}(\sum_d^n \pi_n i^n)\, LSTD_{t-i} + \sum_{i=0}^{11}(\sum_d^n \tau_n i^n)\, LSTN_{t-i} + \epsilon_{(i-1)*52+t}$$

Bayesian model specification was completed by specifying prior distributions for all model parameters. A non-informative normal prior distribution was assumed for the regression coefficients, a Gamma distribution with mean 1 and variance 100 for the parameter, r, an

inverse gamma prior distribution with mean 10 and variance 100, for σ^2 and σ^2, i.e. $\sigma^2 \sim Ga(0.1,0.001), j = 1, \ldots 4$ and a Uniform prior distribution for ρ, i.e. $\rho \sim U[-1,1]$.

Bayesian stochastic variable selection

A spike and slab variable selection algorithm was set up to choose the most optimal polynomial model order most suitable for explaining malaria-climatic variability for each climatic covariate in each endemic setting. For rainfall or any climatic factor, we let $\mathbf{H}_{135*12}$ denote a matrix where the rows represent weeks 1,…,135 and the columns represent the observations of each covariate for lag 0 to lag 11. Let also $\mathbf{K}_{12*5}$ denote a matrix whose rows represent lags (0-12), and columns represent parameters of up to order 4 of the polynomial function describing the lag weights ($\emptyset_n$) where columns 1,2,3,4, and 5 represent parameters for polynomial functions of orders zero, one ($\emptyset_1$), two ($\emptyset_2$), three ($\emptyset_3$), and four ($\emptyset_4$), respectively.

We denote $\boldsymbol{L_{135*5}}$ the matrix product of $\boldsymbol{H}$ and $\boldsymbol{K}$**.** The columns of $\boldsymbol{L}$ represent the polynomial restricted observations of the rainfall data representing of up to order 4. The matrix was then set up in the Bayesian variable selection using a stochastic search with the columns as variables representing the respective polynomial orders A categorical variable $\mathrm{X_p}$ was introduced into the model and assigned values 1 to 5 representing exclusion of the variable from the model $(\mathrm{I_p} = 1)$ equivalent to order zero, and inclusion of the six variables as follows; order one $(\mathrm{I_p} = 2)$, order two $(\mathrm{I_p} = 3)$, order three $(\mathrm{I_p} = 4)$, order four $(\mathrm{I_p} = 5)$. $\mathrm{I_p}$ has a probability mass function $\prod_{\mathrm{j}=1}^{5} \pi_{\mathrm{j}}^{\delta_{\mathrm{j}}(\mathrm{I_p})}$, where π_{j} denotes the inclusion probabilities of functional form j (j=1,2,3,4,5) so that $\sum_{\mathrm{j}=1}^{5} \pi_{\mathrm{j}} = 1$ and $\delta_{\mathrm{j}}(.)$ is the Dirac function, $\delta_{\mathrm{j}}(\mathrm{I_p}) = \begin{cases} 1, & \text{if } \mathrm{I_p} = \mathrm{j} \\ 0, & \text{if } \mathrm{I_p} \neq \mathrm{j} \end{cases}$. A spike and slab prior distribution was assumed for the regression coefficients.

In particular for the coefficient $\beta_{\mathrm{p,l}} \sim \delta_2(\mathrm{I_p})\mathrm{N}(0, \tau_{\mathrm{p,l}}^2) + (1 - \delta_2)\mathrm{N}(0, \vartheta_0 \tau_{\mathrm{p,l}}^2)$ was assumed

for the scenario of selecting one out of four polynomial orders or exclusion of the variable. The coefficients $\{\beta_{p,l}\}_{l=1,..,5}$ corresponding to inclusion of X_p, p=1,…,5 in the model. For inclusion probabilities, a non-informative Dirichlet distribution was adopted with hyper parameter $\alpha = (1,1,1,1,1)^T$, that is, $\boldsymbol{\pi} = (\pi_1, \pi_2, \pi_3, \pi_4, \pi_5)^T \sim \text{Dirichlet}(5, \alpha)$. We also assumed inverse Gamma priors for the precision hyper parameters τ_p^2 and $\tau_{p,l}^2$, $l = 1, \ldots, 5$.

Chapter 8.0: General discussion

We developed Bayesian spatio-temporal models for malaria surveillance in Uganda. These models were used to determine the spatio-temporal changes of malaria burden during 2009-2017, and to assess the effects that malaria interventions, climatic changes, and health facility readiness on the disease distribution. Furthermore, polynomial distributed lag models with high predictive performance were developed to forecast malaria outbreaks in different endemic settings of the country. We analyzed various data sources including routinely collected health facility data reported in the HMIS/DHIS2, weekly surveillance data, nationally representative household surveys, such as Malaria Indicator Surveys (MIS) and Demographic Health Surveys (DHS), health facility assessment surveys, climatic data from remote sensing sources, and national population and housing census.

8.1 Significance of the work

The thesis comprises of six objectives addressed in chapters 2-7. Each chapter includes a discussion of findings. In this section, a general discussion is provided on the contribution and significance of key findings to epidemiological methods and malaria epidemiology in general.

8.1.1 Epidemiological methods

In Chapters 2 and 3**,** we developed spatially varying coefficients models to estimate interventions' effects at subnational scale and to account for potential interactions of interventions with endemicity level. Intervention effects varied with region indicating that interventions do not have the same effect across the country. These models provide crucial information for decision making that enables targeted interventions implementation unlike national scale model estimates that ignore possible heterogeneities in interventions' effects at subnational scale.

In Chapter 3, we developed Bayesian geostatistical and temporal models following earlier work by Giardina (Giardina et al., 2014) to fit data collected from two surveys that

were conducted at different time periods in different locations. To overcome this obstacle, geographical misalignment of the locations between the two surveys was carried out by predicting parasitaemia risk of the first survey at the locations of the second survey. The models were fitted on the MIS 2009 and MIS 2014/15 to determine spatio-temporal trends of parasitaemia risk changes during 2009-2014 and the effects of interventions at national and subnational scales. This methodology is relevant for endemic countries particularly in SSA that periodically conduct national household surveys (MIS and DHS) to monitor malaria burden and intervention coverage over time.

In Chapter 4, we fitted Bayesian spatio-temporal conditional autoregressive negative binomial models on malaria incidence data reported during 2013-2016 by extending models by Rumisha (Rumisha et al., 2013) and Karagiannis-Voules (Karagiannis-Voules et al., 2013). In this thesis, we allowed spatio-temporal patterns of disease incidence to vary from year to year by including year-specific, spatially structured and unstructured random effects modeled at district level via conditional autoregressive and Gaussian exchangeable prior distributions, respectively. This approach is more robust and relevant for malaria situation in Uganda and other endemic countries because space-time patterns of malaria burden differ from year to year due to changes in environmental/climatic factors, interventions and socio-economic transformation. This improves common model formulations for malaria incidence which assumes stable geographical patterns across years.

In Chapters 4 and 5, we applied Bayesian CAR models to obtain district-level estimates of intervention coverage, health-seeking behavior indicators, and socioeconomic indicators from population-based surveys whose samples are calculated to produce precise estimates only for domains of region and country. This approach can be used for studies using data from population-based surveys that wish to estimate predictor effects at a scale that is smaller than the domains considered in for sample size estimation.

Furthermore, in Chapter 5, we developed Bayesian spatio-temporal models to assess the effects of climatic changes on malaria incidence rates changes between 2013 and 2017. The changes in the incidence rates were modeled on the log scale as a function of the difference in climatic conditions between 2013 and 2017, the effects of intervention coverage, socioeconomic status, and the proportion of malaria treatment-seeking behavior in 2017.

In chapter 6, we fitted Bayesian geostatistical models to assess the effects of health facility readiness on severe malaria outcomes. A multidimensional facility readiness index was created using multiple correspondence analysis based on the most important readiness indicators identified using stochastic search geostatistical variable selection. Our methodology used more than one dimension of the MCA to create a robust index unlike in previous studies that used PCA (Boyer et al., 2015; Gage et al., 2016b; Jackson et al., 2015; Oyekale, 2017; Wang et al., 2010), a dimension reduction method for continuous data (Howe et al., 2012), or other studies that used MCA but based on only the first dimension (Ayele et al., 2014; Kollek and Cwinn, 2011). Our study is the first in the epidemiological research domain to incorporate variable selection and use more than one MCA dimension for constructing a multidimensional facility readiness index. Our approach has improved the robustness of the index and made hypothesis testing meaningful as it consists of the most relevant indicators for the outcome and also explains a higher proportion of the variation in the original data compared to the one-dimensional index based on the first dimension. The methodology is applicable in health facility assessment surveys where a need arises to develop a single indicator of readiness that is representative of the vast array of readiness indicators defined from health facility performance/readiness.

Malaria forecasting models were developed in Chapter 7 using polynomial distributed lag terms (Teklehaimanot et al., 2004a) to relate malaria incidence and climatic predictors. We used stochastic variable selection to identify the optimal polynomial order of the climatic

factors in each endemic setting. To the best of our knowledge, this is the first malaria forecasting study that has selected the optimal polynomial function in different endemic settings. Results highlighted varying degrees of malaria burden in the country and different order of polynomial models required in each setting. This implies that a decentralized forecasting system that takes into consideration the local endemicity levels and ecological settings will be required as opposed to one system. These models can serve as a foundation for setting up and operationalizing a Malaria Early Warning System (MEWS) to facilitate the forecasting of malaria outbreaks and allow for planning and timely deployment of response interventions.

8.1.2 Malaria epidemiology

In this section, the contribution of this thesis to malaria epidemiology in Uganda and other similar endemic settings of SSA is discussed.

8.1.2.1 Malaria decline and resurgence

The malaria risk and incidence maps produced from this thesis illustrate the contemporary malaria situation in the country and show considerable shrinkage in malaria burden from 2009 to 2015, and a resurgence in 2016. These maps can serve as important tools for decision making support, resource mobilization, planning and targeted implementation of interventions, monitoring and evaluation of malaria control activities in Uganda.

Malaria burden at least up to until 2015 coincided with an accelerated scale-up of vector control interventions and case management with ACTs (Uganda Bureau of Statistics and ICF International, 2015), improving socioeconomic conditions and health services delivery (Uganda Bureau of Statistics (UBOS), 2017). In spite of this reduction attained in most of the regions over time, malaria transmission remains high and uninterrupted in the regions of East Central, North East and West Nile. These findings are in agreement with results reported from a field study that reported entomological inoculation rates as high as

310 infectious bites per year in these regions (Kamya et al., 2015). The high transmission rates in some areas could explain why Uganda still ranks among the top six countries with the highest number of *Plasmodium falciparum* infections in the world (World Health Organisation, 2017).

The disturbing trend of malaria resurgence in the country starting in 2016 is similar to trends observed at the global scale - more than 5 million cases were reported in 2016 compared to 2015. This upsurge in Uganda may be explained by changes in climatic conditions (Jagannathan et al., 2012), loss of population-level immunity as a result of sustained high intervention coverage (Ghani et al., 2009), cessation of IRS activities in the high burdened mid-north region (President's Malaria Initiative, 2017), and the influx of one million refugees from South Sudan due to political conflicts (UNHCR, 2017).

8.1.2.2 Interventions' effects

The work in this thesis has demonstrated that malaria interventions, that is, ITNs, IRS, and ACTs have played a major role in the reduction of malaria burden in Uganda. These interventions have been recommended by WHO in endemic settings for malaria control and prevention due to their ability in reducing human-vector contact (Spitzen et al., 2017), direct killing of mosquitoes (CDC, 2018), and rapid clearance of malaria parasites in the population (Pousibet-Puerto et al., 2016) for ITNs, IRS and ACTs, respectively. The effectiveness of interventions in Uganda is in agreement with findings from other studies in other endemic settings that reported reduction in malaria case incidence (Lengeler, 2004) and mortality rates (Eisele et al., 2010). Similarly, ITNs and IRS have been reputed for having made a major contribution to the reduction in malaria burden in SSA during 2000-2015 (Bhatt et al., 2015a).

Results also showed that despite the fact that ITN ownership is near universal coverage levels, the use of ITNs has remained inadequate (Uganda Bureau of Statistics and

ICF International, 2015). This could be explained by the weak social mobilization on the part of NMCP to promote the use of ITNs (Taremwa et al., 2017).

Our results demonstrated varying effects of interventions in different regions of the country. This could be explained by heterogeneities in malaria transmission levels, environmental, and socioeconomic conditions. The interplay of these factors requires area specific intervention programming in Uganda as opposed to a one-size-fits-all approach. Whereas in some areas, minimizing host-vector contact is sufficient in lowering transmission by ITNs, in other areas reduction in vector population through IRS will be a prerequisite for a reduction in transmission pressure.

Although the WHO discourages the supplementation of one intervention by another (WHO, 2014), our findings demonstrated that a higher level of malaria decline was achieved in regions/districts where IRS and ITNs were implemented together compared to districts with only ITNs (Uganda Bureau of Statistics and ICF International, 2015). In line with our findings, other studies have also attested to significant transmission interruption and a decline in morbidity in the Mid-North region where the ITNs and IRS interventions were combined (Tukei et al., 2017). Unfortunately, NMCP discontinued IRS in the high-burden districts in the north of the country and has failed to extend this intervention to other high-risk areas in the eastern region (National Malaria Control Program, 2016) resulting in malaria resurgence in the former (Raouf et al., 2017) and consistently high uninterrupted transmission in the latter (Kamya et al., 2015). This slow-paced deployment and scale-up of IRS has been attributed to the high costs involved in its implementation and the high technical capacity of personnel required for spraying activities and monitoring of insecticide side effects (Talisuna et al., 2015).

8.1.2.3 Socioeconomic influence

Our results have shown a positive correlation between malaria burden and poverty in Uganda. The high malaria burden remains disproportionately concentrated in the northern and eastern parts of the country where poverty is high and socioeconomic development the lowest. The high poverty levels in the country may be responsible for high malaria transmission and thus mitigating the success of malaria reduction strategies. Indeed recent studies indicated that the proportion of the population living in poverty in Uganda has increased from 20 percent to 27 percent in the last 10 years, which is equivalent to 10 million people (Uganda Bureau of Statistics (UBOS), 2017). Currently Uganda is number 163 on the Global Human Development Index (GHI) (United Nations Development Program, 2016). The malaria-poverty vicious cycle can be explained by the fact that poverty affects the ability to access treatment services, nutrition, and access to media for malaria prevention awareness messages (Teklehaimanot and Mejia, 2008).

A lower malaria burden was shown in urban areas compared to rural areas. This can be attributed to the urbanization immediate impact on destroying mosquito breeding sites as land is reclaimed for accommodation purposes leading to lower malaria transmission. Our findings concur with other studies in other settings (Wilson et al., 2015). However, these studies have warned that in the long-term, unique mosquito breeding sites develop in urban areas leading to the emergence of urban malaria in major towns and cities – a phenomenon that requires environmental modification interventions which unfortunately have received little attention to date in Uganda (Talisuna et al., 2015).

8.1.2.4 Environmental influence

This work has further demonstrated that climatic changes have had a detrimental effect on malaria reduction gains achieved through accelerated interventions scale-up in Uganda. This finding further augments the evidence that the environment is a key driver of malaria

transmission (Reiner et al., 2015). In Chapters 2-5, results indicated higher malaria burden in cultivated areas compared to areas with no cultivation. This finding is a threat to malaria control activities in Uganda given the country's rapidly growing population (Uganda Bureau of Statistics, 2016) and high-income inequalities (Uganda Bureau of Statistics (UBOS), 2017) that are forcing people to move into previously uninhabitable areas to grow food, a change that is leading to land changes and environmental degradation which ultimately will increase susceptibility to malaria risk (Hall, 2000). Also, the high population pressure in the country has exacerbated rural-urban migration resulting in massive deforestation and cultivation of wetlands, which increases mosquito breeding sites leading to increased malaria transmission (Isunju et al., 2016).

8.1.2.5 Health facility readiness to provide malaria treatment

Study results in Chapter 6 showed that although higher facility readiness was associated with a reduced risk of severe malaria outcomes, facility readiness to provide malaria treatment is still very low in Uganda These results point to a weak health system which may help explain high latent reservoir of parasitaemia risk in the population.

8.1.2.6 Model-based malaria early warning system

The predictive performance of the forecasting models developed in this thesis is high and this could be attributed to the robustness of the polynomial functions that were used in model development to capture the complex non-linear relationship between malaria and climatic factors similar to what has been reported in field experiments (Bayoh and Lindsay, 2003; Christiansen-Jucht et al., 2014, 2015a). These high predictive performance models can be used by National Malaria Control Program as a building block for effective model-based malaria early warning system to forecast outbreaks and thus allow for enough time for planning and allocation of resources in affected areas.

8.2 Limitations and challenges

Though the introduction of the DHIS2 has improved reporting of routine facility data, nevertheless, systemic issues that undermine complete data reporting from all facilities still remain. Most importantly is the weakly supervised and regulated private sector which means that several private facilities don't report in the HMIS leading to underreporting and hence underestimation of malaria burden in the country. In the public sector where reporting rates are high and consistent, a substantial proportion is not parasitologically confirmed especially in lower level facilities owing to diagnostic weaknesses (Kyabayinze et al., 2012). This may lead to overestimation of the malaria burden in the country.

The application of CAR models in Chapters 4 and 5 may bias parameter estimates due to the ecological fallacy (Jenkins et al., 2015). The remedy to this problem is the application of the point process models such as log-Gaussian Cox model (Diggle et al., 2013) which produce precise parameter estimates. However, their application requires direct analysis of case locations which are not available in the current DHIS2 system. Instead, the data is reported in aggregate form at the catchment area of the health facility which can only be analyzed using CAR models.

8.3 Conclusion and recommendations

The work in this thesis is very important for malaria surveillance in Uganda and the methods can be applied to other endemic countries. The results can inform evidence-based implementation of malaria prevention, control and treatment activities and future programming in the country. The malaria risk maps and other estimates produced are vital for evaluation of the effects of interventions, environmental/climatic factors and understanding the role that health facility readiness has had on malaria burden reduction in Uganda at national and subnational scales. This in turn will inform priority setting, decision making, resource mobilization, timing, and targeted deployment of interventions to maximize benefits

and optimizing resources for achieving the goals set in country and international malaria reduction and elimination frameworks.

Nonetheless, the malaria per capita funding in Uganda which stands at less than US$ 1 is inadequate for interrupting malaria transmission to achieve pre-transmission phase as desired in the national and international frameworks. Therefore to further sustain malaria reduction and avert the recent upsurge in Uganda, NMCP should lobby government, international and local donors for more funding to implement an integrated vector management package to interrupt malaria transmission, as well as add other tools to the repertoire of malaria control in Uganda such as mass drug administration and intermittent prevention treatment for infants in the high-burden areas. In the same vein, the government should prioritize poverty alleviation programs to boost socioeconomic development to break the vicious cycle of poverty that undermines the progress of malaria control activities. In line with this, the government should fulfill its obligation of allocating at least 17% of its national budget to the health sector as per Abuja declaration agreement to help address the fragile health system that hinders malaria treatment.

In order to strengthen monitoring and evaluation of malaria activities in Uganda, NMCP needs to build capacity in the state-of-the-art methods such as Bayesian geostatistical and spatio-temporal models that have been developed in this thesis through collaboration with national and international research and academic institutions. Also, NMCP should create synergies with other sectors whose activities overlap with malaria control activities particularly the agricultural and National Meteorological Authority (NMA). The NMA has capacity in weather forecasts and environmental monitoring and can assist NMCP to develop a MEWS which is a key intervention missing in malaria surveillance in Uganda.

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Curriculum vitae

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2. Personal profile

A Biostatistician trained in Bayesian and frequentist approaches and their applications in epidemiology and public health.

Proficient and experienced in the following statistical modelling and inference areas: Bayesian modelling and analysis, Geostatistical modelling, Areal modelling, Spatio-temporal modelling, Geospatial / spatial analysis, Hierarchical modelling / multi-level models, Time series analysis, Random effects models, Longitudinal data analysis, Complex surveys design and analysis, Meta-analysis, Clustered data analysis, Epidemiological study design and analysis, Survival analysis, Multivariate statistics, Remote sensing data processing and modelling, stochastic variable selection.

Possesses excellent statistical computing, data analysis and database management skills in the following software; R, STATA, WINBUGS/OpenBUGS, INLA, STAN, JAGS, ArcGIS, QGIS, GenStat, SPSS, Visual basic, MS Access, CSPro, Epi-Info, Epi data, SQL server.

3. Research interests

Main epidemiological research interests include development of Bayesian hierarchical models in infectious diseases epidemiology with special interest in malaria, HIV/AIDS and Tuberculosis, and neglected tropical diseases to assess environmental, socioeconomic, and

interventions' effects on spatio-temporal changes in resource limited settings; Disease mapping for determination of geographical distribution of health outcomes and targeted public health interventions; Development and application of surveillance methods to detect outbreaks of infectious diseases; Application of multivariate statistics techniques in health systems strengthening measurements and assessment of their effects on health outcomes; Development of forecasting models for infectious diseases

4. Education Background

Institution	**Degree**	**Period**
Swiss, Tropical and Public Health Institute, University of Basel, Switzerland	PhD, Epidemiology (Bayesian modeling and analysis)	2015-2018
Makerere University Kampala, Uganda	Master of Statistics (Biostatistics)	2008-2011
Makerere University Kampala, Uganda	Bachelor of Statistics	2001-2004

5. Work Experience

Sept 2017 – June 2018	Tutor of Advanced statistical modelling and Bayesian statistics semester courses, Swiss, Tropical and Public Health Institute, University of Basel, Switzerland
Jan 2015 - to date	Part time lecturer of Biostatistics, Makerere University, School of Public Health, Department of Epidemiology and Biostatistics
Jan 2014 - June 2017	Head of Statistics and Data management, International AIDS HIV Vaccine Program, Entebbe, Uganda
Sept 2011-Dec 2013	Monitoring and Evaluation Coordinator / Senior Data Manager, UN Millenium Villages project – Ruhiira Mbarara, Uganda
Jan 2011 - Aug 2011	Monitoring and Evaluation Coordinator, Makerere University Joint AIDS Program, Kampala, Uganda
Jan 2010 - Dec 2010	Monitoring and Evaluation officer, Makerere University Joint AIDS Program, Kampala, Uganda
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Nov 2004 - Dec 2005	Data officer, Makerere University Joint AIDS Program, Kampala, Uganda

6. Peer-reviewed publications

Ssempiira J, Kissa J, Nambuusi B, Mukooyo E, Opigo J, et al. Towards model-based development of malaria early warning system to predict outbreaks in Uganda. *PLoS One* 2018 (submitted)

Ssempiira J, Kissa J, Kasirye I, Nambuusi B, Mukooyo E, et al. Assessing the effects of health facility readiness on severe malaria outcomes in Uganda. *BMC Health services research* 2018 (submitted)

Ssempiira J, Kissa J, Nambuusi B, Mukooyo E, Opigo J, et al. Interactions between climatic changes and intervention effects on malaria spatio-temporal dynamics in Uganda. *Parasite Epidemiology and Control.* 2018, doi:10.1016/j.parepi.2018.e00070

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7. Professional development

May 2018: The messenger is the message, *University of Basel, Switzerland*

April 2018: Discover and manage your scientific literature, *University of Basel, Switzerland*

April 2018: Citation, Paraphrase or Plagiarism, *University of Basel, Switzerland*

March 2018: Peer Reviewing in Natural and Life Sciences: From Submission to Retraction, *University of Basel, Switzerland*

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March 2018: Peer coaching – Generating ingenious solutions in nine set steps, *University of Basel, Switzerland*

March 2018: Writing Productivity: Tools and Techniques, *University of Basel, Switzerland*

February 2018: Optimizing Research Data management, *University of Basel, Switzerland*

November 2017: GIS for Public Health, *Swiss School of Public Health, Switzerland*

October 2017: Multilevel Modeling; Analysis of Clustered Data, *Swiss School of Public Health, Switzerland*

June - Oct 2017: Survey Sampling Online Training, *The Demographic and Health Surveys program, USA*

July 2017: Applied Bayesian statistics in medical research, *Institute of Social and Prevention Medicine, Bern, Switzerland*

May 2017: Missing data in epidemiology: implications and analysis techniques, *University of Basel, Switzerland*

April 2017: Essentials in health research methodology, *University of Basel, Switzerland*

February 2017: Essentials in health research methodology, *University of Basel, Switzerland*

November 2016: Walking in the Editor's shoes: Peer reviewing and journal editing for young

researchers in health sciences, *Swiss TPH, University of Basel, Switzerland*

Feb – May 2016: Writing to be published for the natural sciences, *University of Basel, Switzerland*

April 2016: Malaria epidemiology and control**,** *Swiss TPH, University of Basel, Switzerland*

Feb-May 2016: Bayesian statistics, *Swiss TPH, University of Basel***,** *Switzerland*

March 2016: Introduction to the statistical software R, *University of Basel***,** *Switzerland*

Oct-Dec 2015: Bayesian hierarchical modeling, *University of Basel***,** *Switzerland*

Dec 2014: Systematic reviews and Meta-analysis, *Makerere University College of Health Sciences, Uganda*

July 2014: Project planning and management, *Africa Mentoring Institute, Uganda*

June 2014: Advanced Statistical methods in epidemiology, *Medical Research Council/Uganda Virus Research Institute*

April 2014: Good Clinical Practice, *Africa Research Initiative and Support – Network.*

June 2014: Human Subjects protection, Columbia University

June 2010: ArcView based Geographic Systems, *GIS Consult, Kampala, Uganda*

Jan 2009: Introduction to Research proposal writing and data management workshop – Clinical operations and health services research, *Joint Clinical Research Centre, Uganda*

Oct 2008: Medical informatics, Clinical operations and health services research, *Joint Clinical Research Centre, Uganda*

Aug 2008: Designing and administering of MS SQL server 2000 Enterprise edition, *New Horizons, Kampala, Uganda*

July 2008: HIV Quality improvement Training, *Ministry of Health and HIVQUAL-Uganda*

Aug 2007: Monitoring and Evaluation of ARV Supply chain management system, *Medical Access, Kampala, Uganda*

May 2007: Programming using Visual Basic, *Techno Brains ltd, Uganda*

Nov 2006: Monitoring and Evaluation for performance improvement, *California STD/HIV Prevention Training Center, Kampala, Uganda*

May 2006: Effective oral presentation skills, *Makerere University IPH-CDC Program, Kampala, Uganda*

Referees

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